Supplementary information

[2+1+1] Assembly of spiro β-lactams by Rh(II)-catalyzed reaction of diazocarbonyl compounds with azirines/isoxazoles

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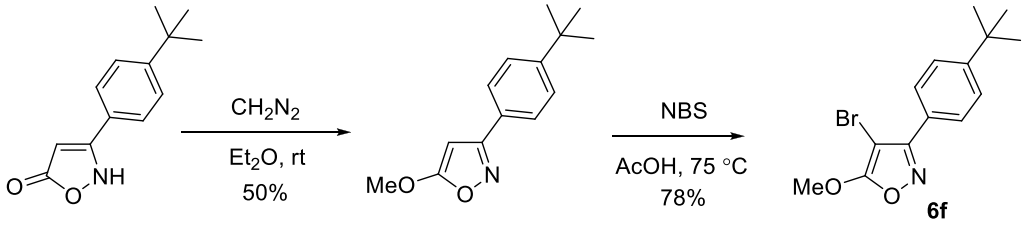
1. General experimental details

Melting points were determined on a melting point apparatus SMP30. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE 400 spectrometer in $CDCl_3$. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Electrospray ionization (ESI), positive mode, mass spectra were measured on a Bruker MaXis mass spectrometer. Thin-layer chromatography (TLC) was conducted on aluminum sheets precoated with SiO_2 ALUGRAM SIL G/UV254. Column chromatography was performed on Macherey-Nagel silica gel 60 M (0.04–0.063 mm). Dichloromethane was washed with concentrated H_2SO_4, water, then distilled from P_2O_5 and stored over anhydrous K_2CO_3.

2. Synthesis of 4-bromo-3-(4-*tert*-butylphenyl)-5-methoxyisoxazole 6f[1]

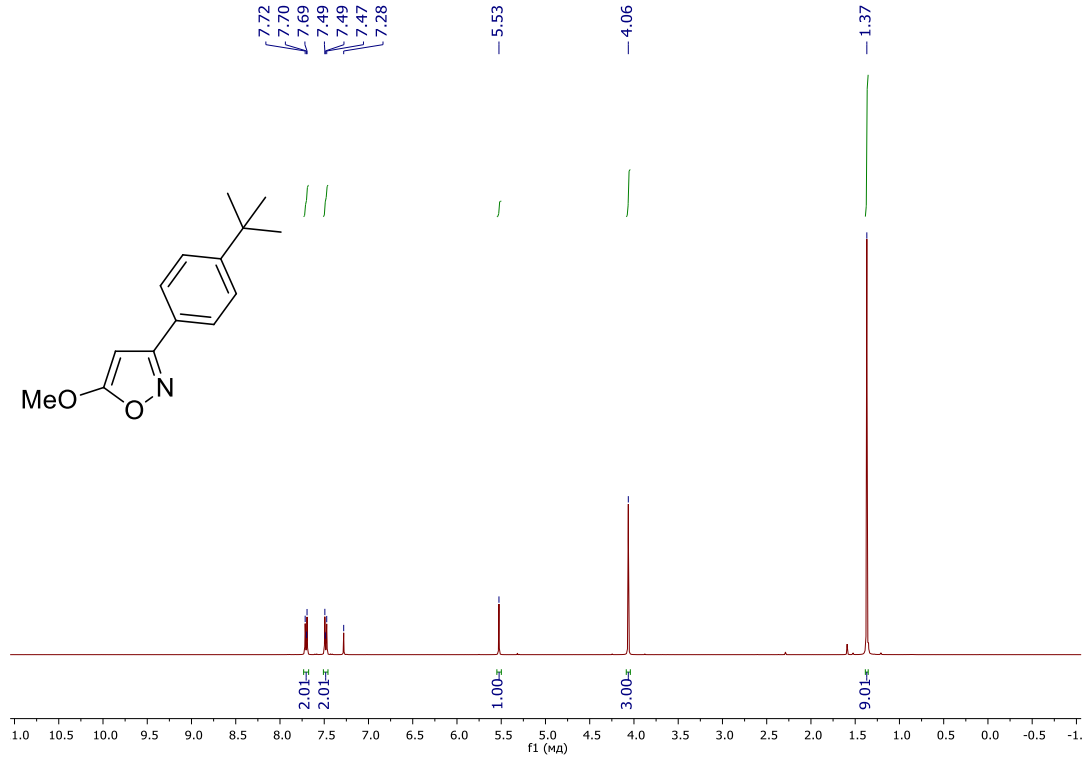


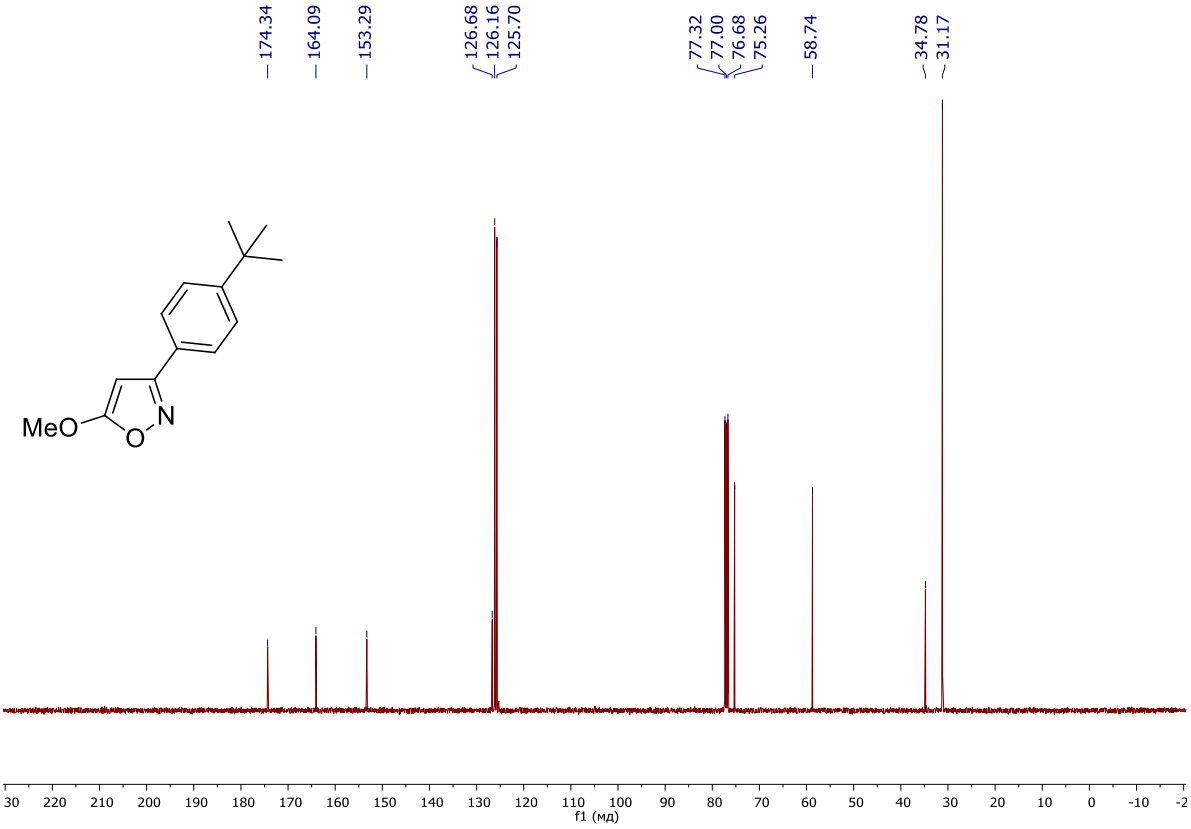
Synthesis of 3-(4-tert-butylphenyl)-5-methoxyisoxazole. To a stirred suspension of 3-(4-(*tert*-butyl)phenyl)isoxazol-5(4*H*)-one (1.22 g, 5.6 mmol) in anhydrous Et_2O (50 mL) was added dropwise at 0 °C a solution of diazomethane (11.2 mmol) in Et_2O, prepared from *N*-nitroso-*N*-methylurea (1.73 g, 16.8 mmol) and KOH (5.02 g, 89.6 mmol). The resulting mixture was stirred at ambient temperature for 2 h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexane) to give 3-(4-*tert*-butylphenyl)-5-methoxyisoxazole (648 mg, 50%) as a colorless solid. Mp 74−76 °C (Et_2O–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.68 (m, 2H), 7.51–7.46 (m, 2H), 5.53 (s, 1H), 4.06 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 164.1, 153.3, 126.7, 126.2, 125.7, 75.3, 58.7, 34.8, 31.2. HRMS−ESI $[M+H]^+$ calcd for $C_{14}H_{18}NO_2^+$: 232.1332; found 232.1330.

Synthesis of 4-bromo-3-(4-tert-butylphenyl)-5-methoxyisoxazole. A solution of 3-(4-*tert*-butylphenyl)-5-methoxyisoxazole (462 mg, 2 mmol) and *N*-bromosuccinimide (392 mg, 2.2 mmol) in AcOH (10 mL) was heated at 75 °C under stirring for 40 min. The reaction mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexane) to give isoxazole **6** (484 mg, 78%) as a colorless solid. Mp 87−89 °C (Et_2O–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.76 (m, 2H), 7.54–7.50 (m, 2H), 4.23 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 162.4, 153.5, 127.6, 125.6, 125.4, 66.7, 58.4, 34.9, 31.2. HRMS−ESI $[M+H]^+$ calcd for $C_{14}H_{17}{}^{79}BrNO_2^+$: 310.0437; found 310.0444.

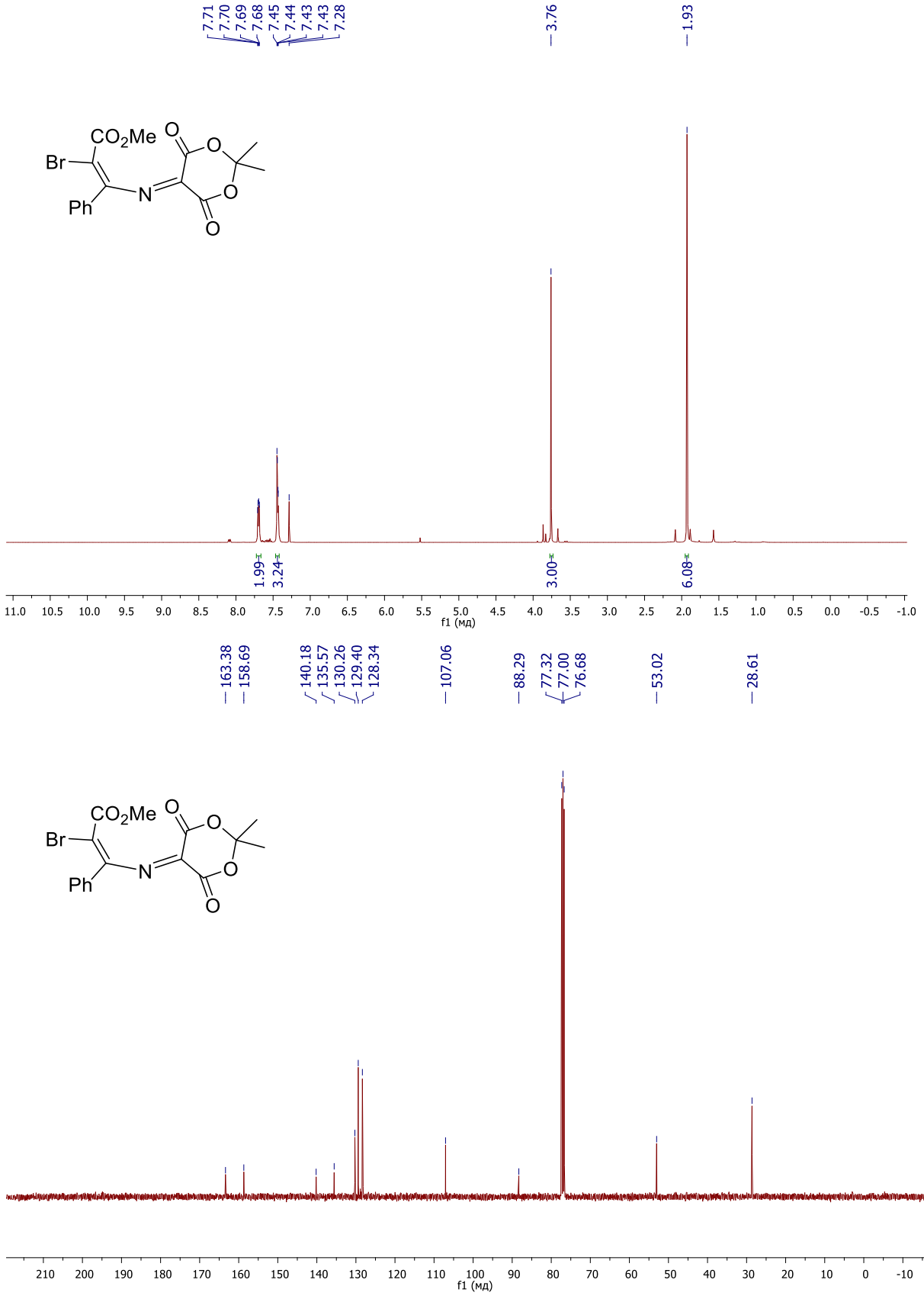
3. ^{1}H and ^{13}C NMR spectra

3-(4-(*tert*-Butyl)phenyl)-5-methoxyisoxazole

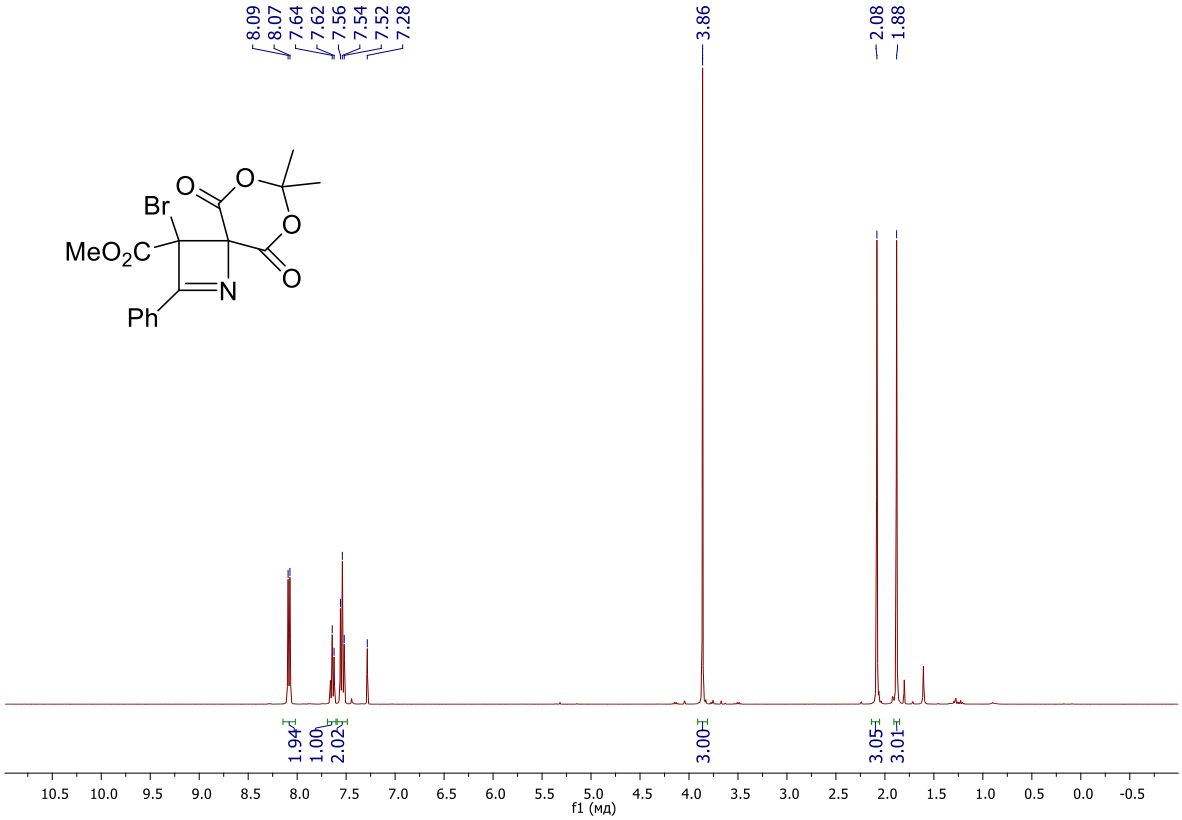


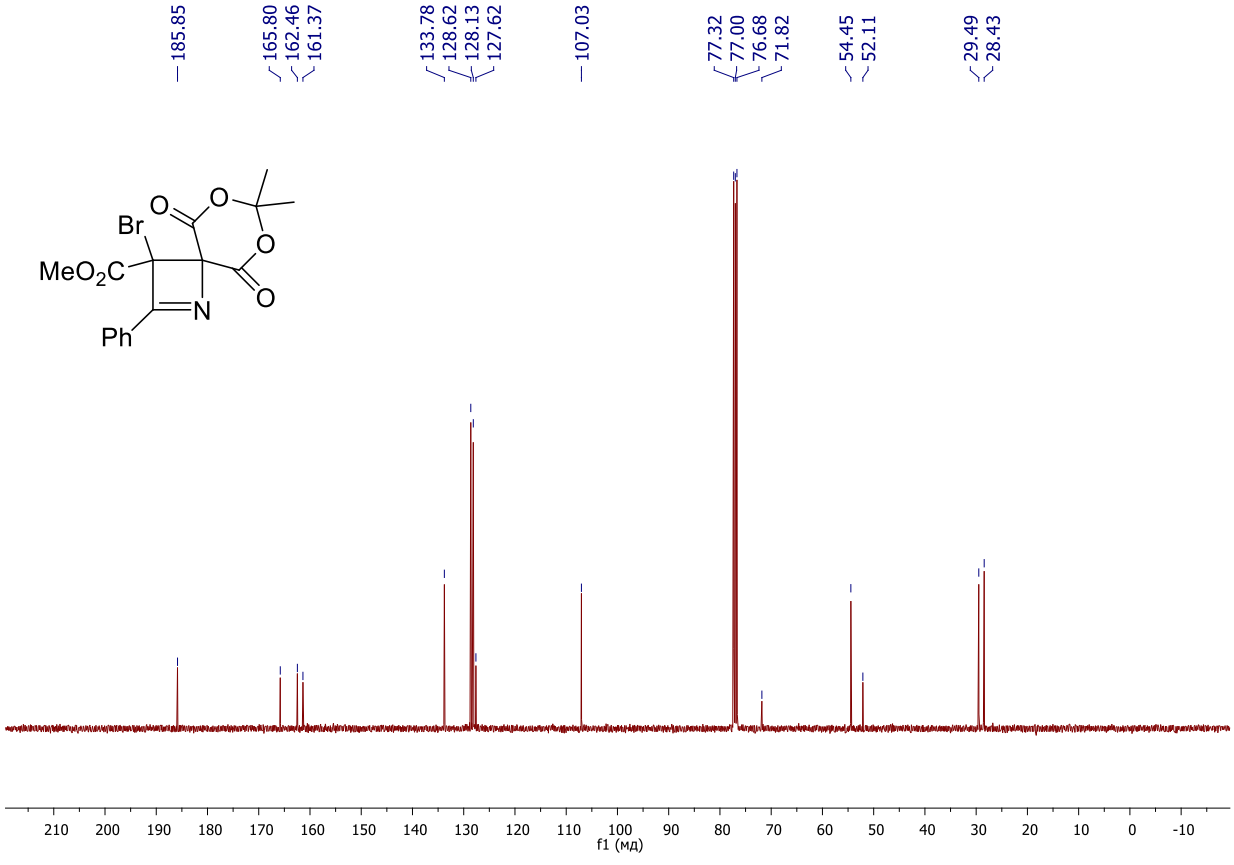


Methyl (*E*)-2-bromo-3-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylideneamino)-3-phenylacrylate (3a)

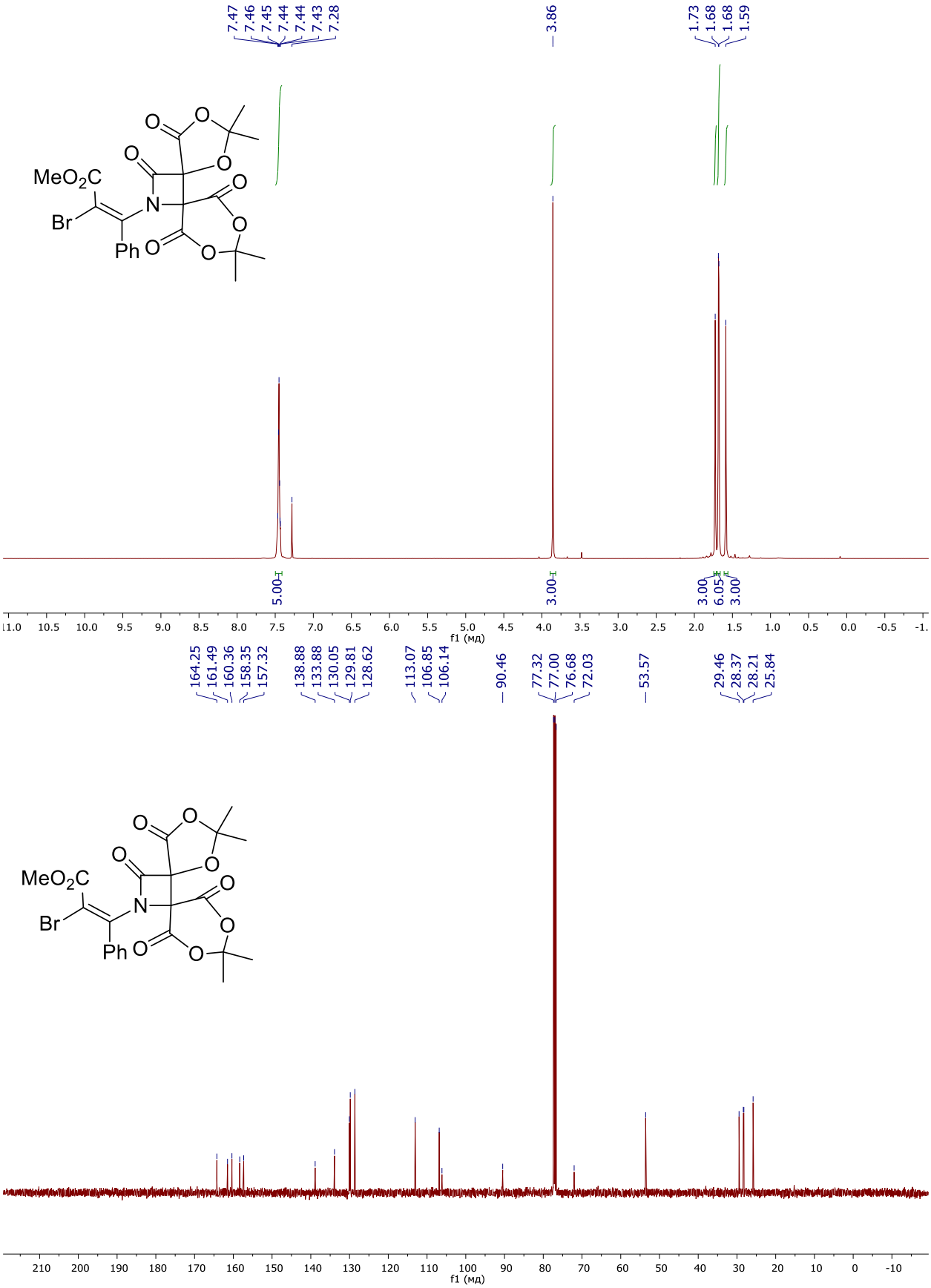


Methyl 3-bromo-7,7-dimethyl-5,9-dioxo-2-phenyl-6,8-dioxa-1-azaspiro[3.5]non-1-ene-3-carboxylate (4a)

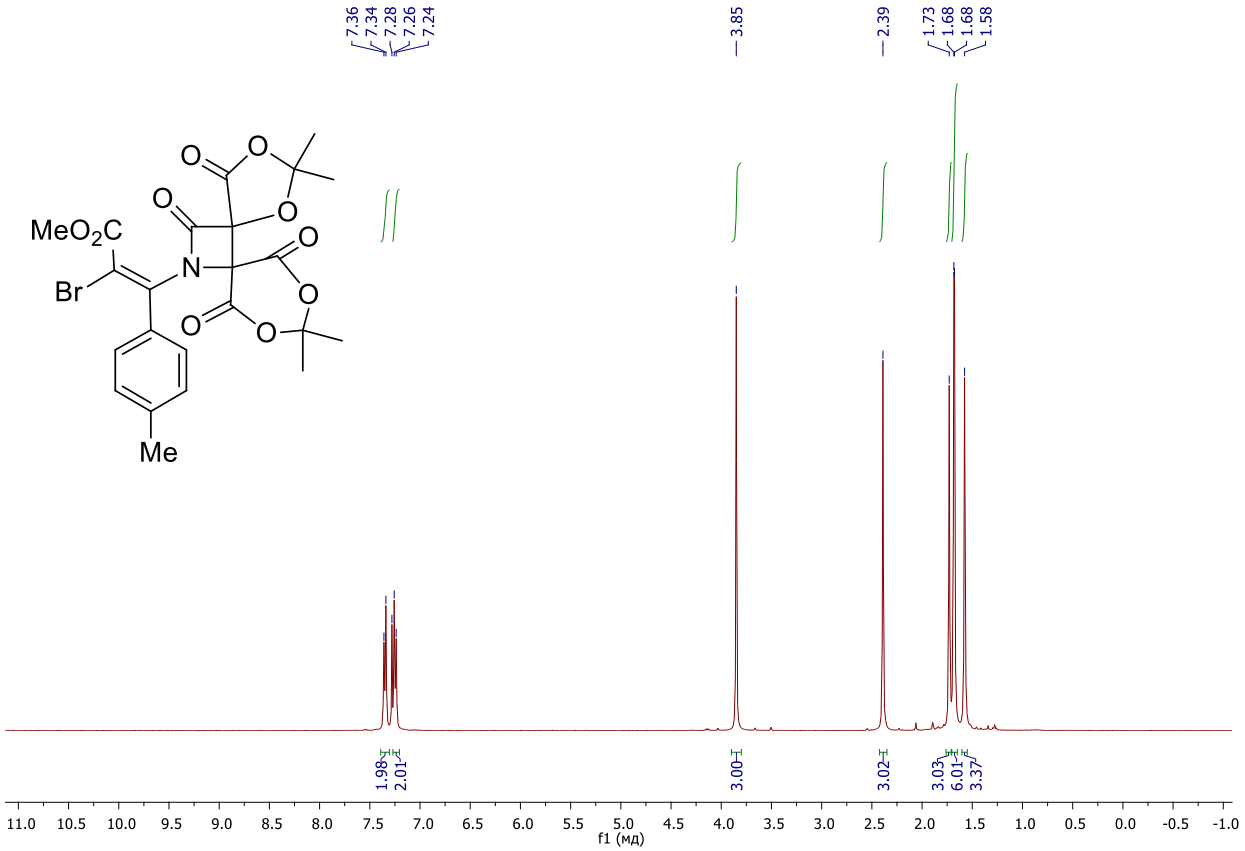


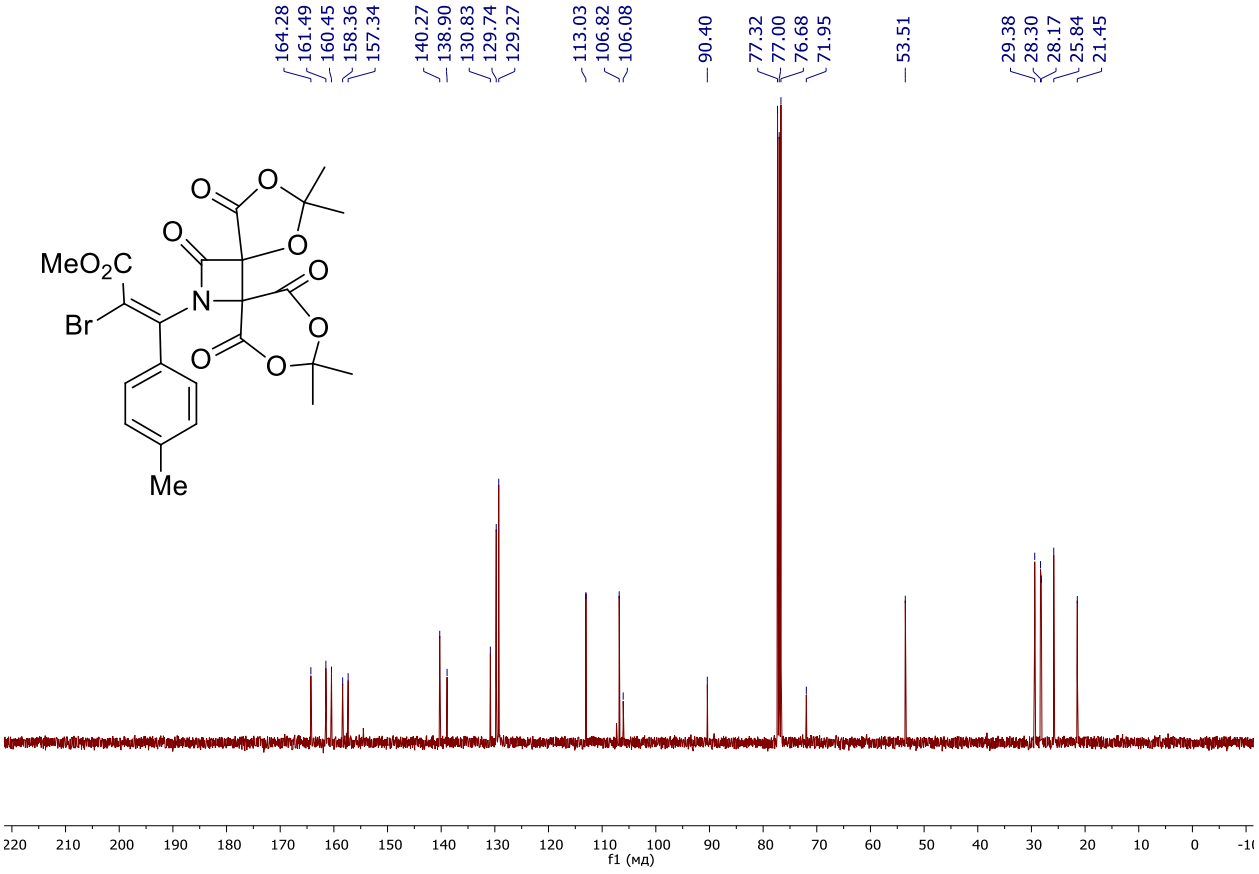


Methyl (*E*)-2-bromo-3-phenyl-3-(2,2,9,9-tetramethyl-4,7,11,13-tetraoxo-1,3,8,10-tetraoxa-12-azadispiro[4.0.5^6.2^5]tridecan-12-yl)acrylate (5a)

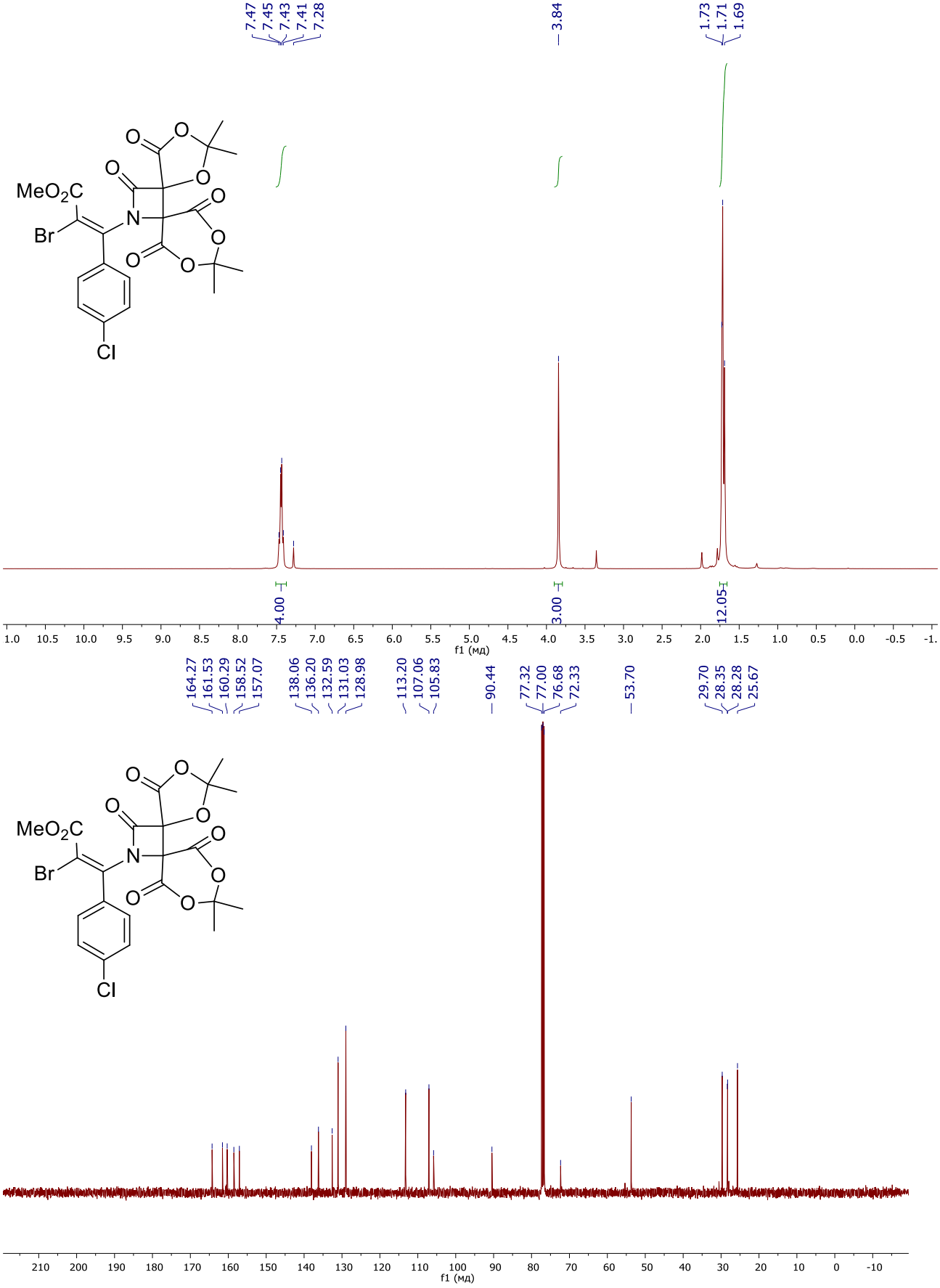


Methyl (*E*)-2-bromo-3-(4-methylphenyl)-3-(2,2,9,9-tetramethyl-4,7,11,13-tetraoxo-1,3,8,10-tetraoxa-12-azadispiro[4.0.5^6.2^5]tridecan-12-yl)acrylate (5b)

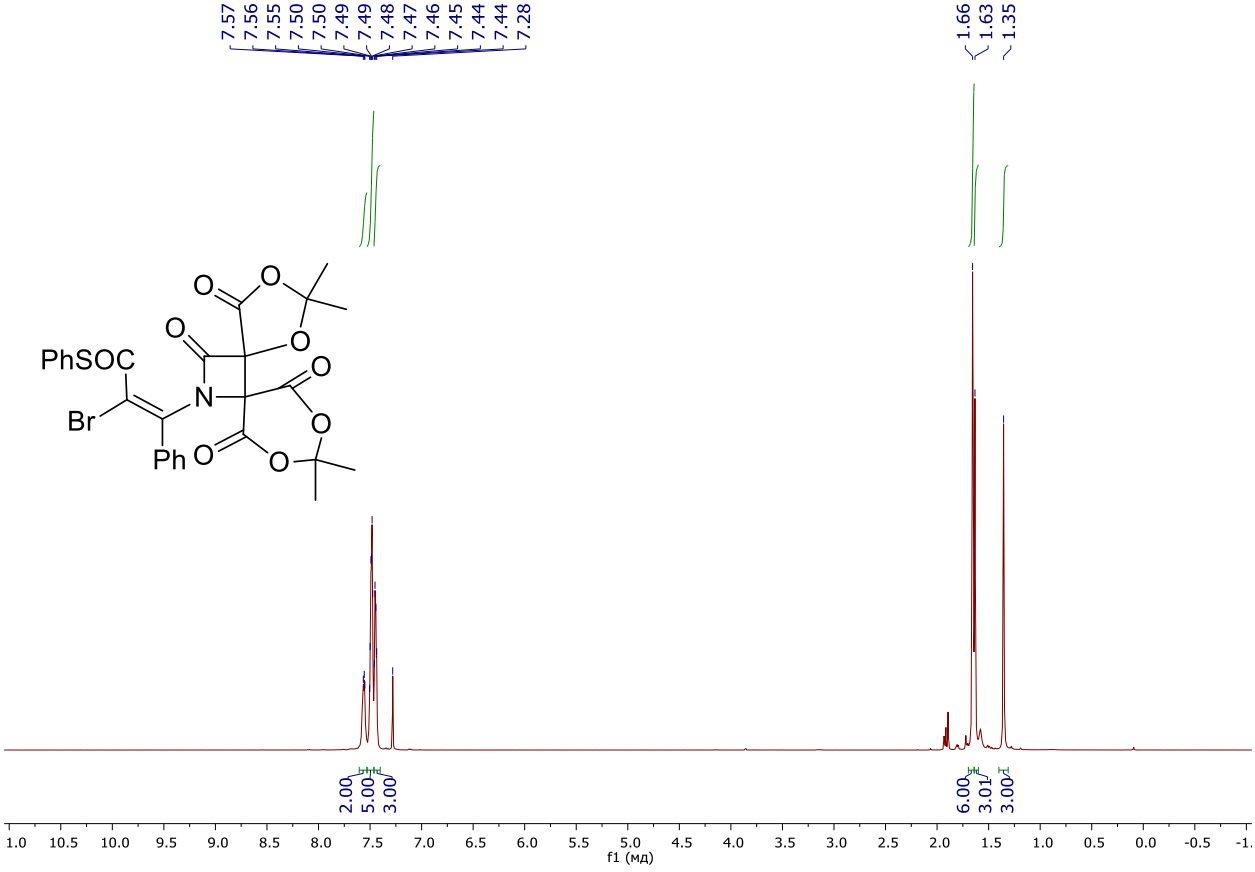


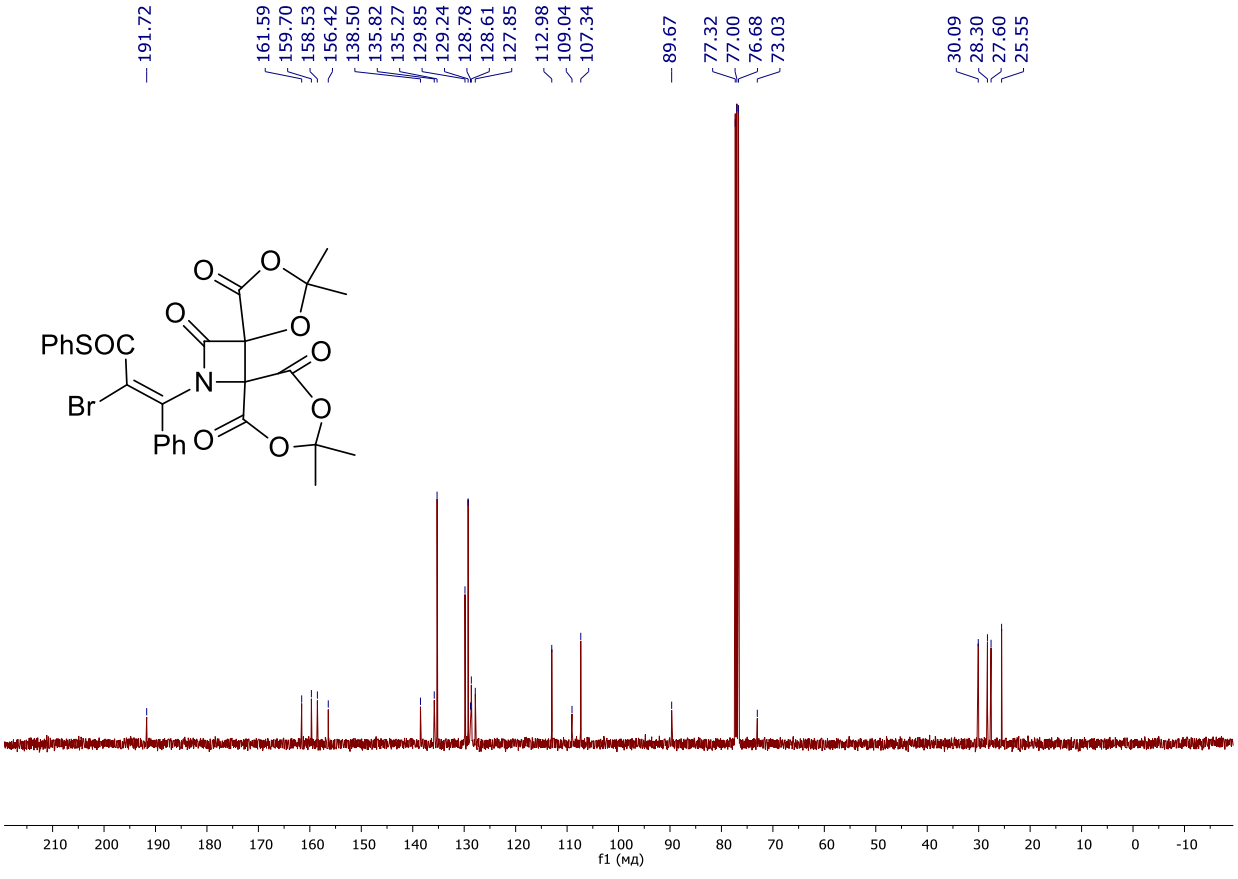


Methyl (*E*)-2-bromo-3-(4-chlorophenyl)-3-(2,2,9,9-tetramethyl-4,7,11,13-tetraoxo-1,3,8,10-tetraoxa-12-azadispiro[4.0.5^{6}.2^{5}]tridecan-12-yl)acrylate (5c)

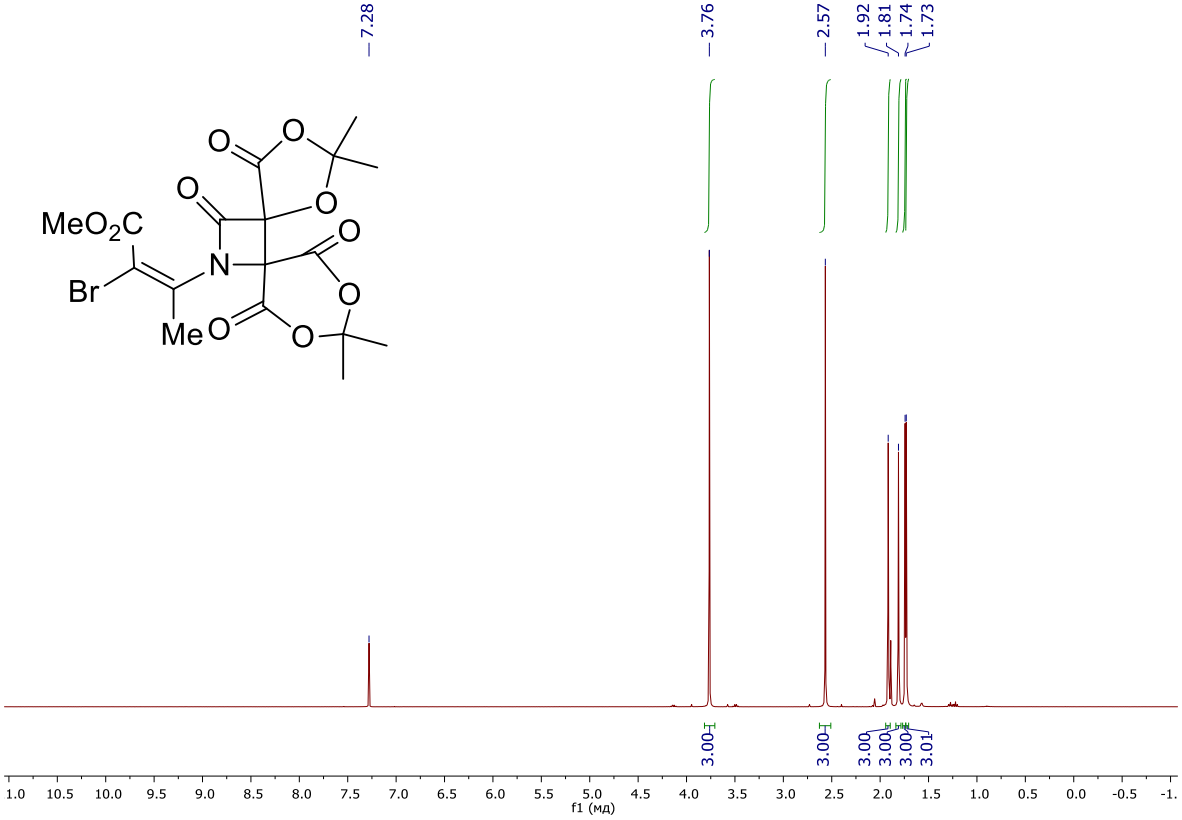


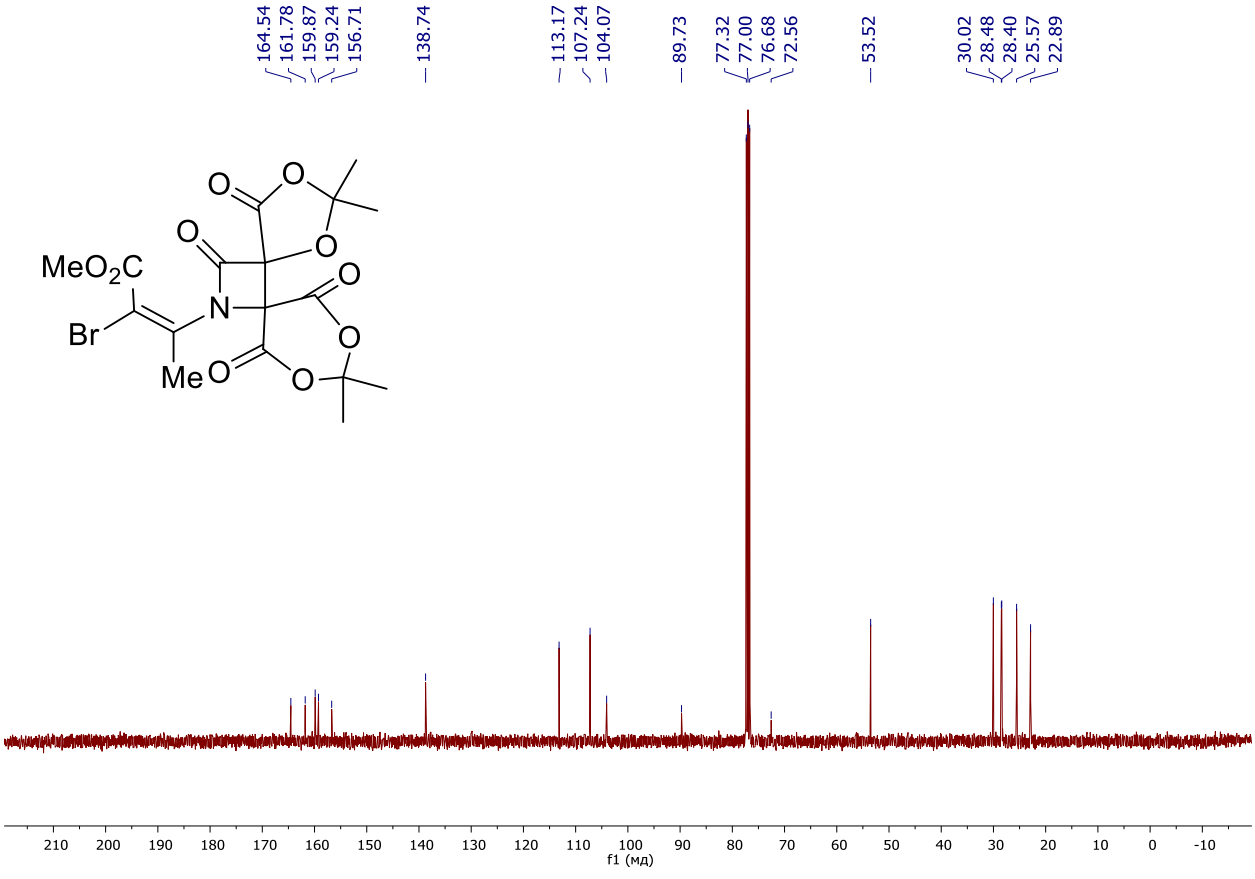
S-Phenyl (*E*)-2-bromo-3-phenyl-3-(2,2,9,9-tetramethyl-4,7,11,13-tetraoxo-1,3,8,10-tetraoxa-12-azadispiro[4.0.5^6.2^5]tridecan-12-yl)prop-2-enethioate (5d)



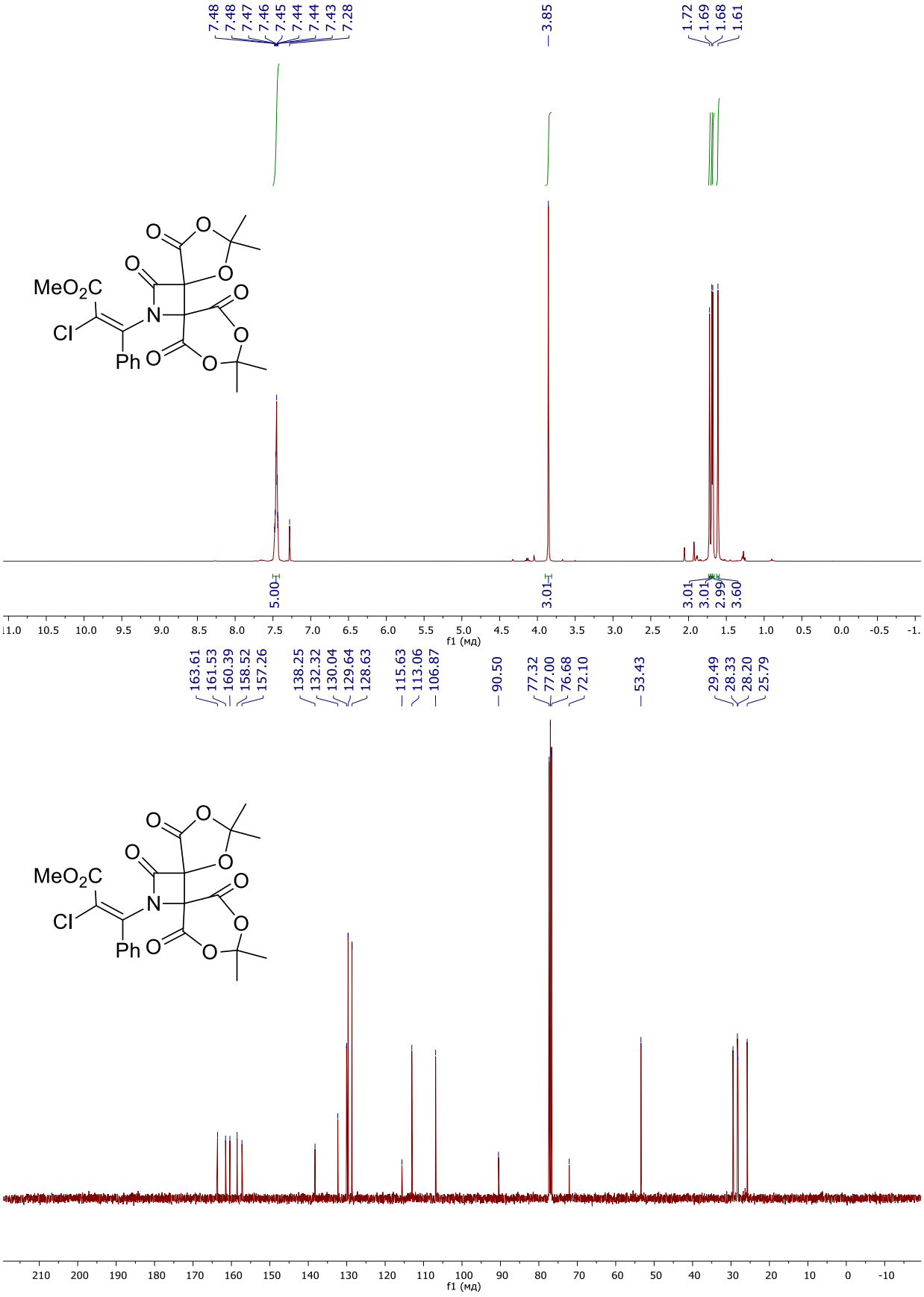


Methyl (*E*)-2-bromo-3-(2,2,9,9-tetramethyl-4,7,11,13-tetraoxo-1,3,8,10-tetraoxa-12-azadispiro[4.0.5^6.2^5]tridecan-12-yl)but-2-enoate (5e)

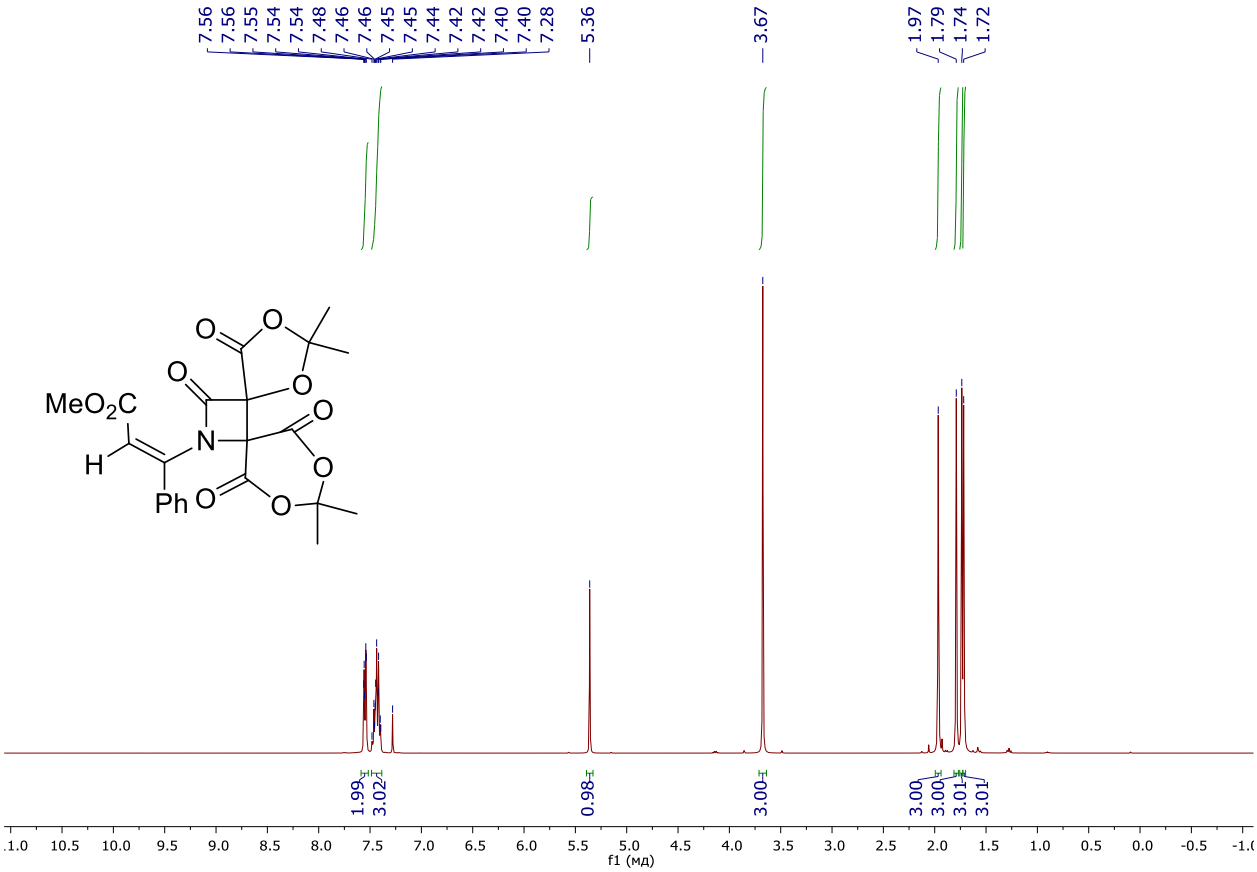


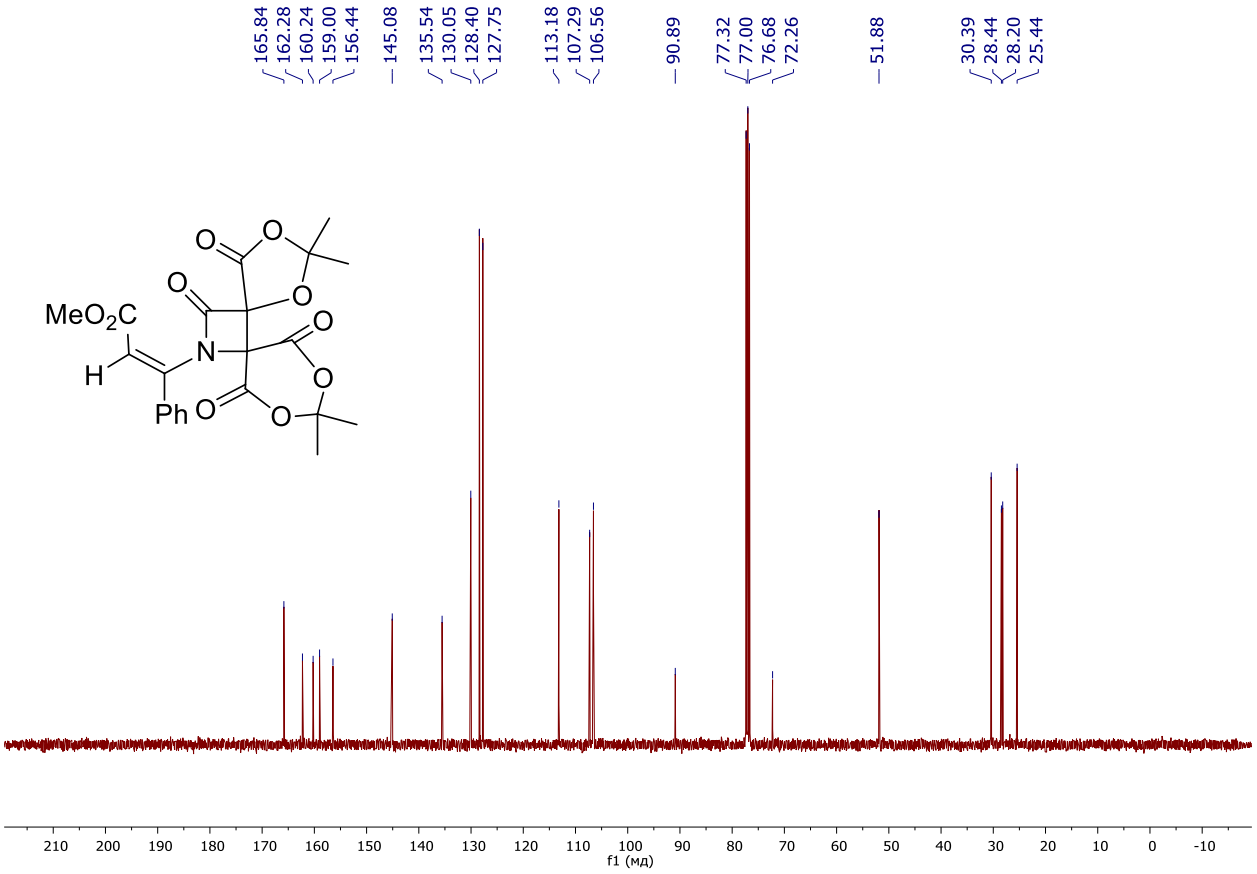


Methyl (*E*)-2-chloro-3-phenyl-3-(2,2,9,9-tetramethyl-4,7,11,13-tetraoxo-1,3,8,10-tetraoxa-12-azadispiro[4.0.5^6.2^5]tridecan-12-yl)acrylate (5f)

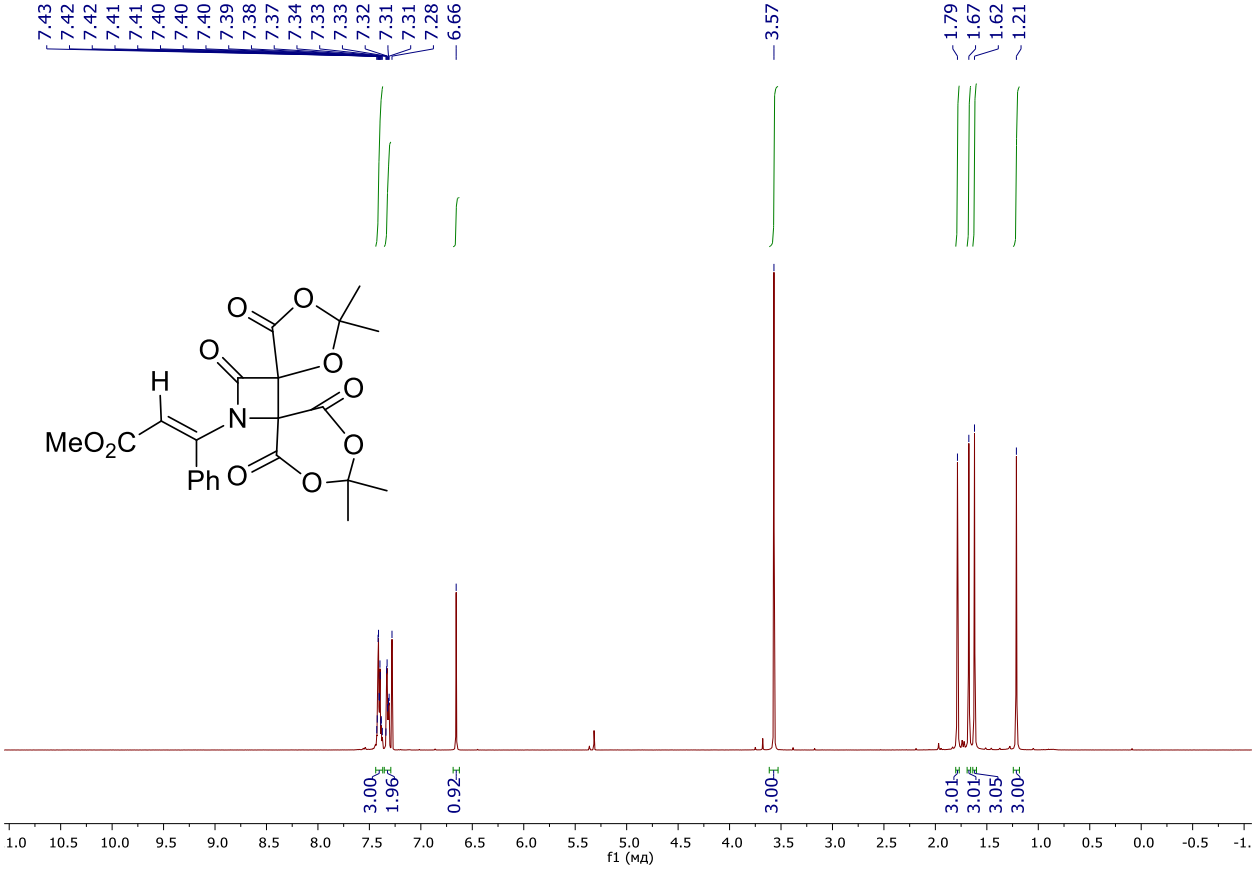


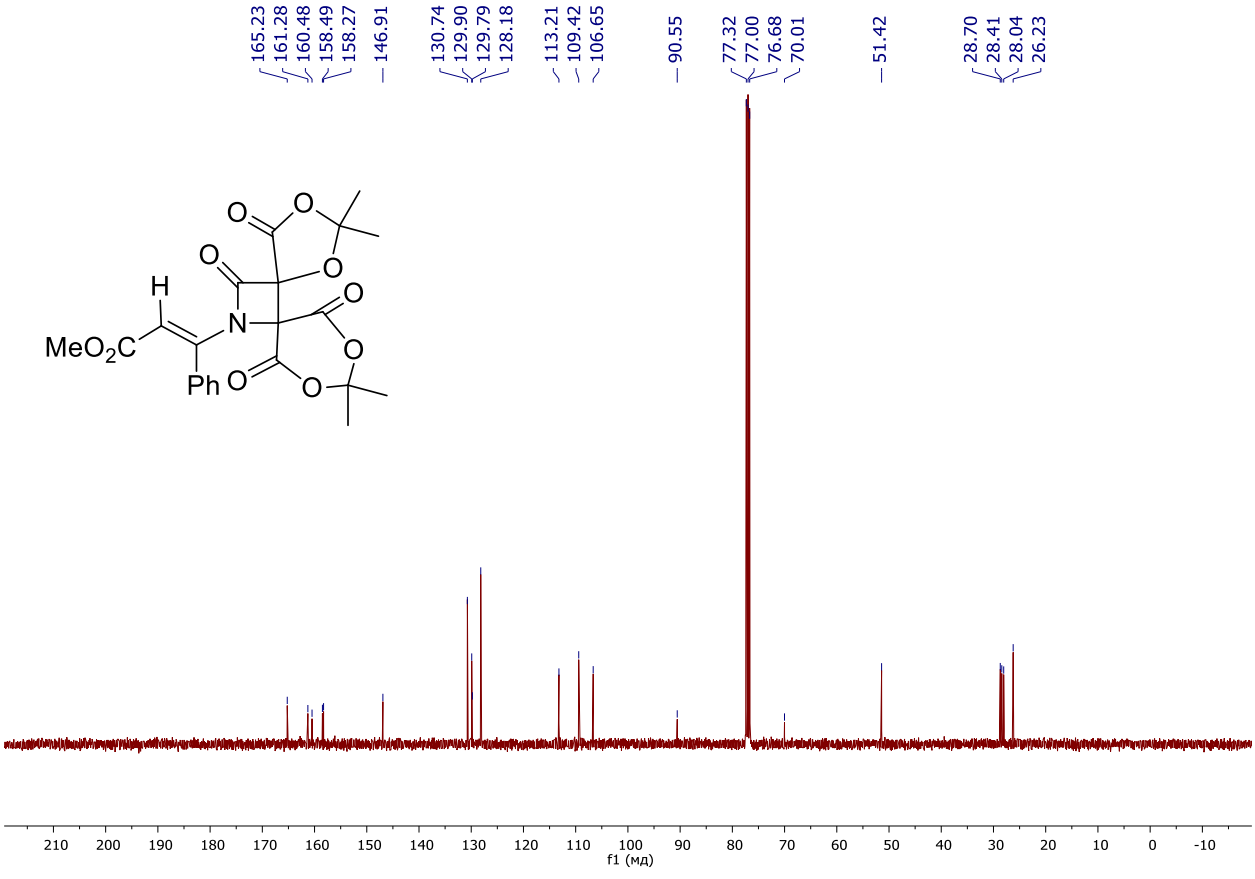
Methyl (*Z*)-3-phenyl-3-(2,2,9,9-tetramethyl-4,7,11,13-tetraoxo-1,3,8,10-tetraoxa-12-azadispiro[4.0.5^{6}.2^{5}]tridecan-12-yl)acrylate (*Z*-5g)



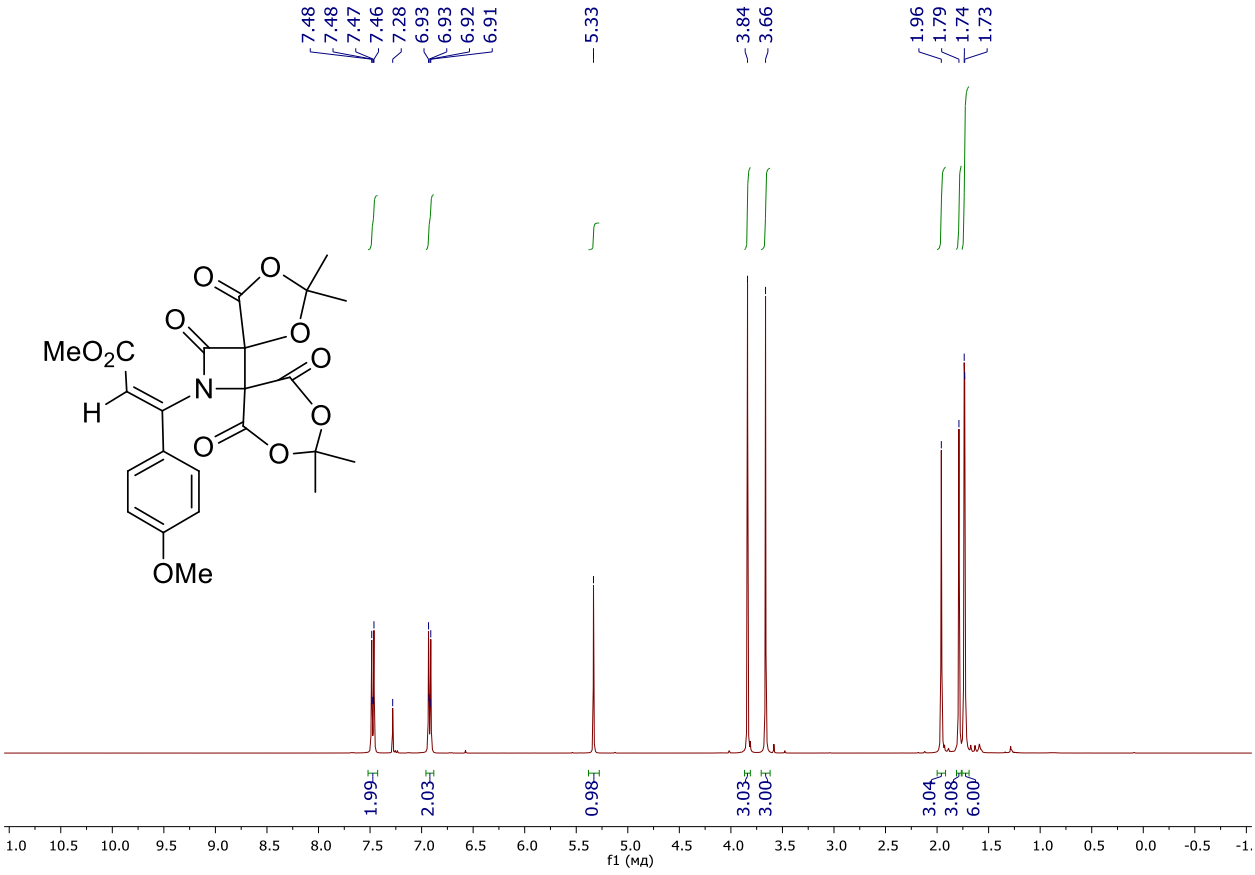


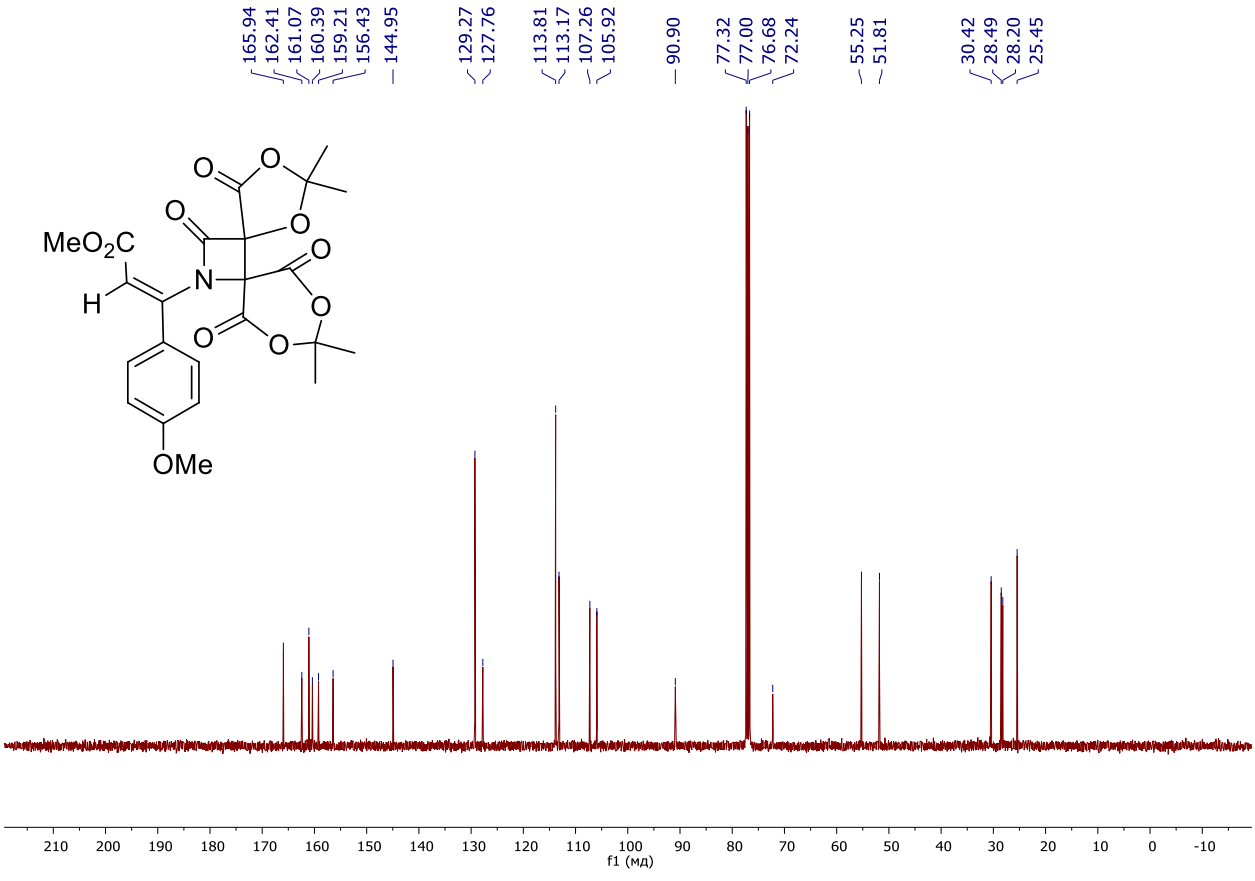
Methyl (*E*)-3-phenyl-3-(2,2,9,9-tetramethyl-4,7,11,13-tetraoxo-1,3,8,10-tetraoxa-12-azadispiro[4.0.5^6.2^5]tridecan-12-yl)acrylate (*E*-5g)



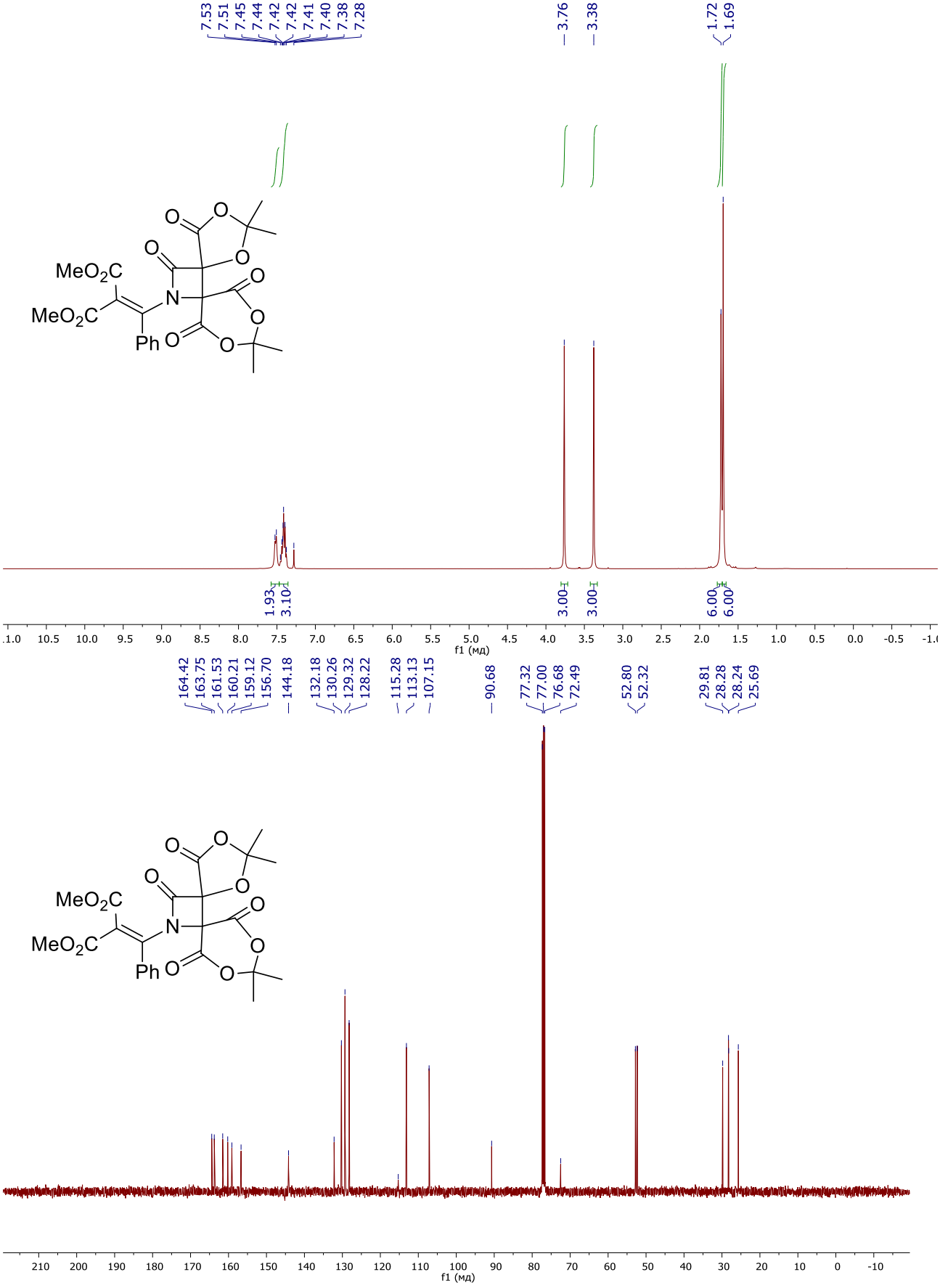


Methyl (*Z*)-3-(4-methoxyphenyl)-3-(2,2,9,9-tetramethyl-4,7,11,13-tetraoxo-1,3,8,10-tetraoxa-12-azadispiro[4.0.5^6.2^5]tridecan-12-yl)acrylate (5h)

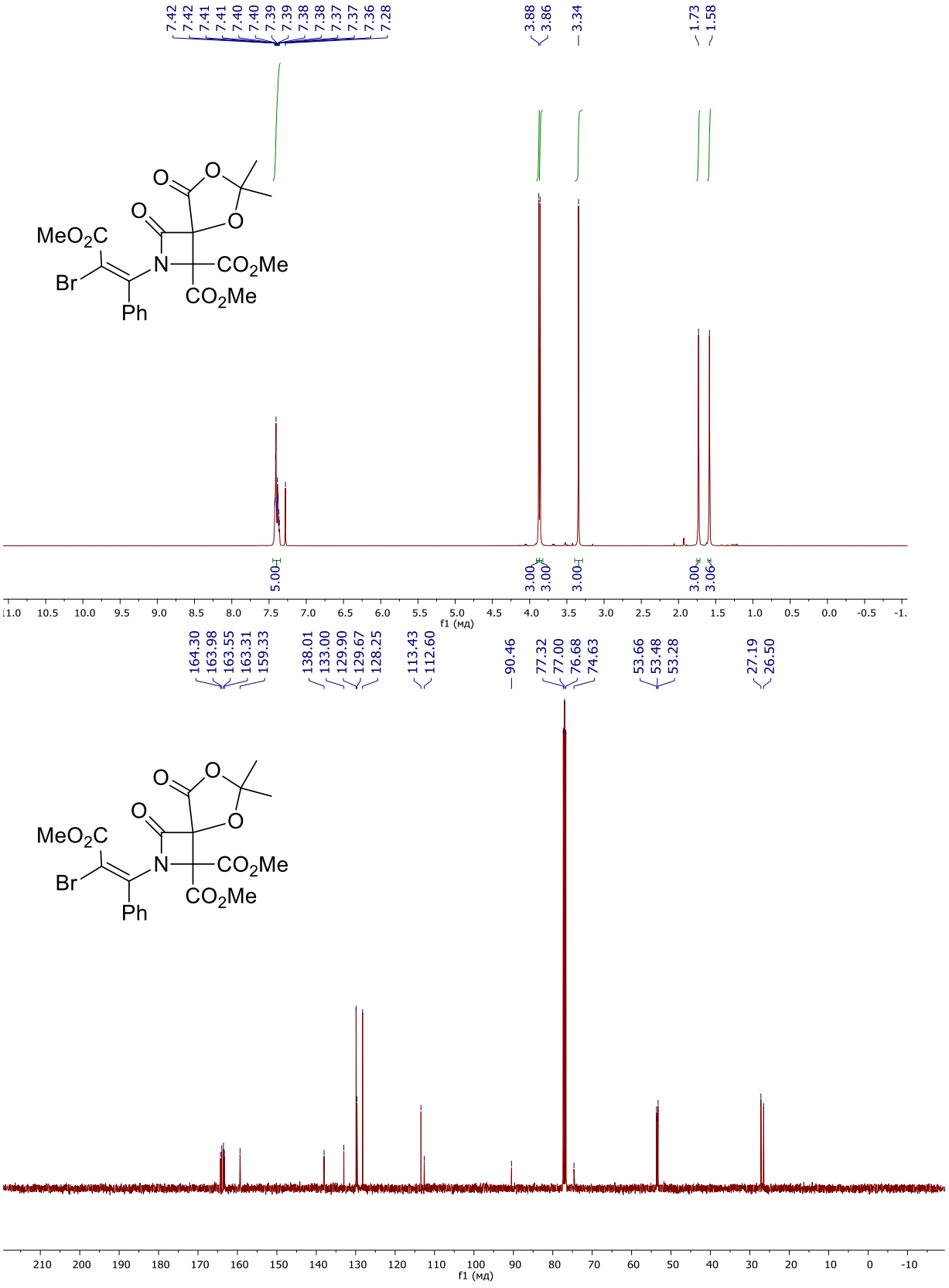




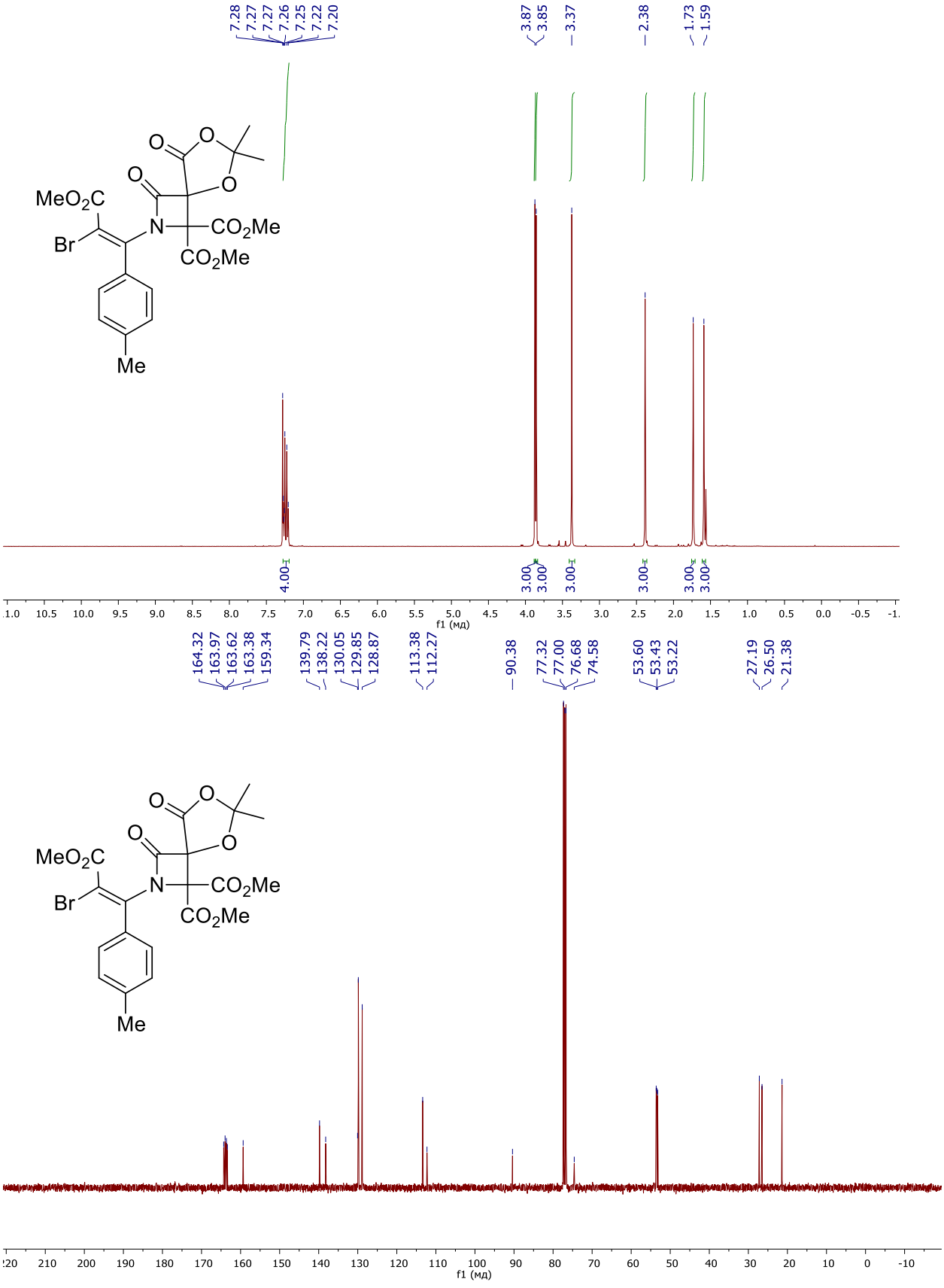
Dimethyl 2-(phenyl(2,2,9,9-tetramethyl-4,7,11,13-tetraoxo-1,3,8,10-tetraoxa-12-azadispiro[4.0.5^{6}.2^{5}]tridecan-12-yl)methylene)malonate (5i)



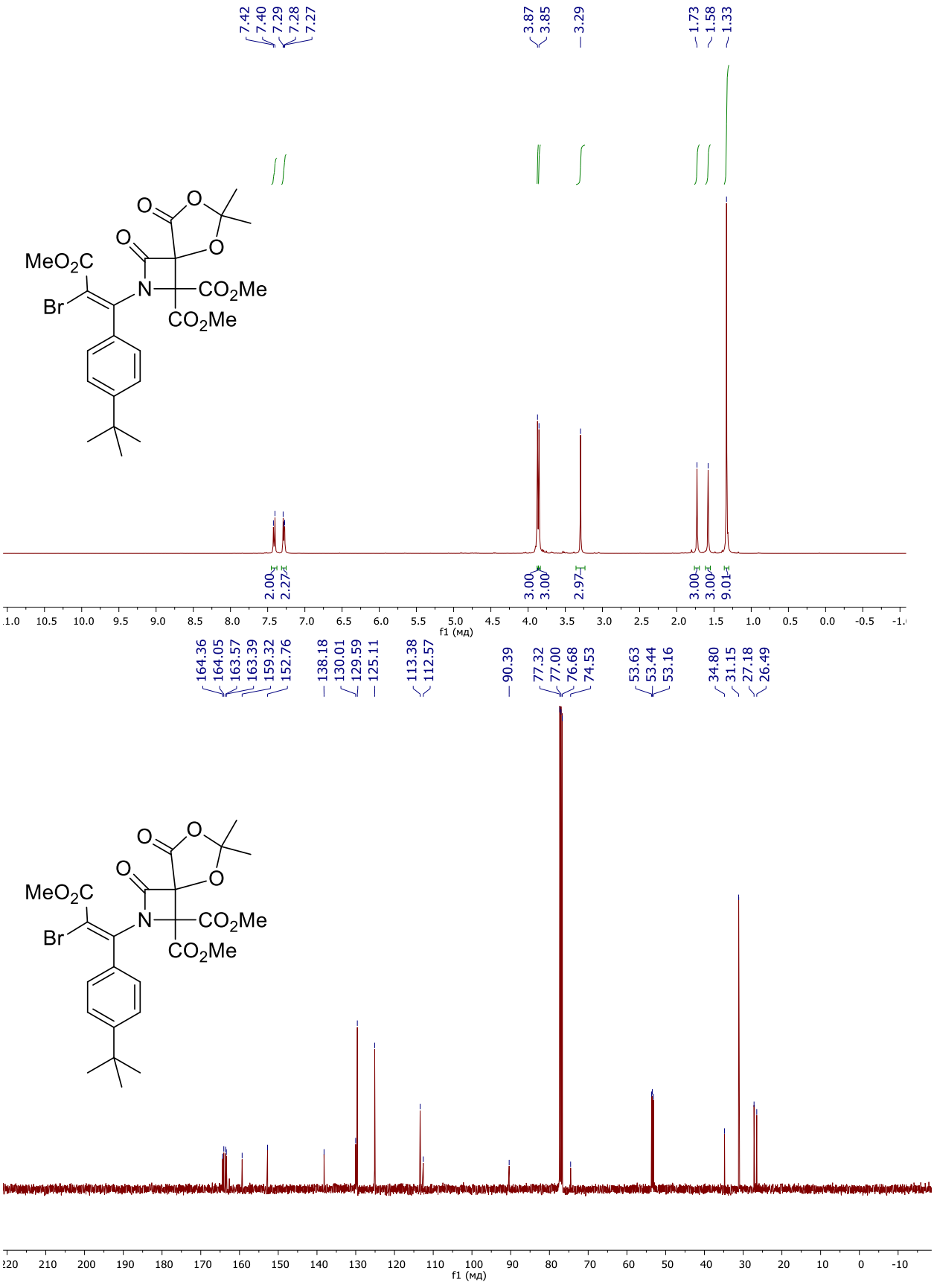
Dimethyl *(E)*-2-(2-bromo-3-methoxy-3-oxo-1-phenylprop-1-en-1-yl)-6,6-dimethyl-3,8-dioxo-5,7-dioxa-2-azaspiro[3.4]octane-1,1-dicarboxylate (5j)



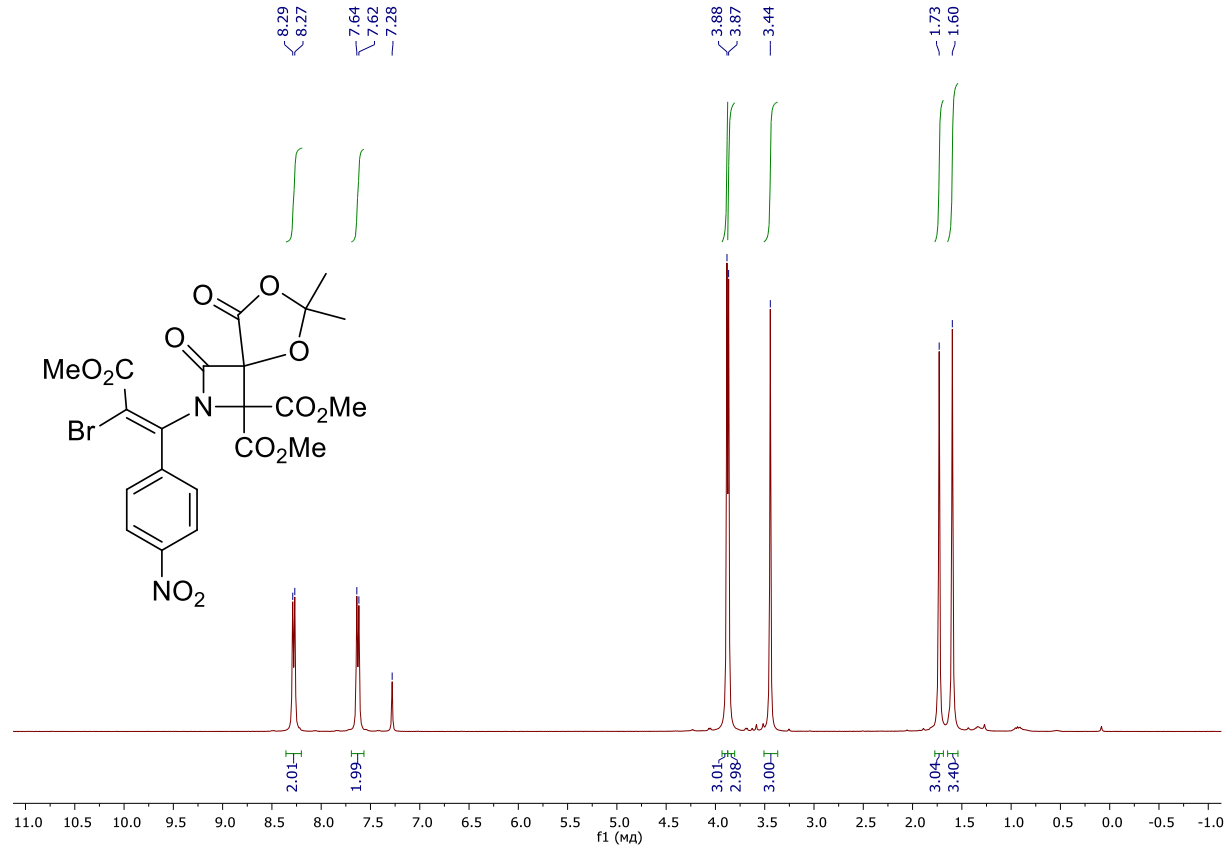
Dimethyl *(E)*-2-(2-bromo-3-methoxy-3-oxo-1-(p-tolyl)prop-1-en-1-yl)-6,6-dimethyl-3,8-dioxo-5,7-dioxa-2-azaspiro[3.4]octane-1,1-dicarboxylate (5k)

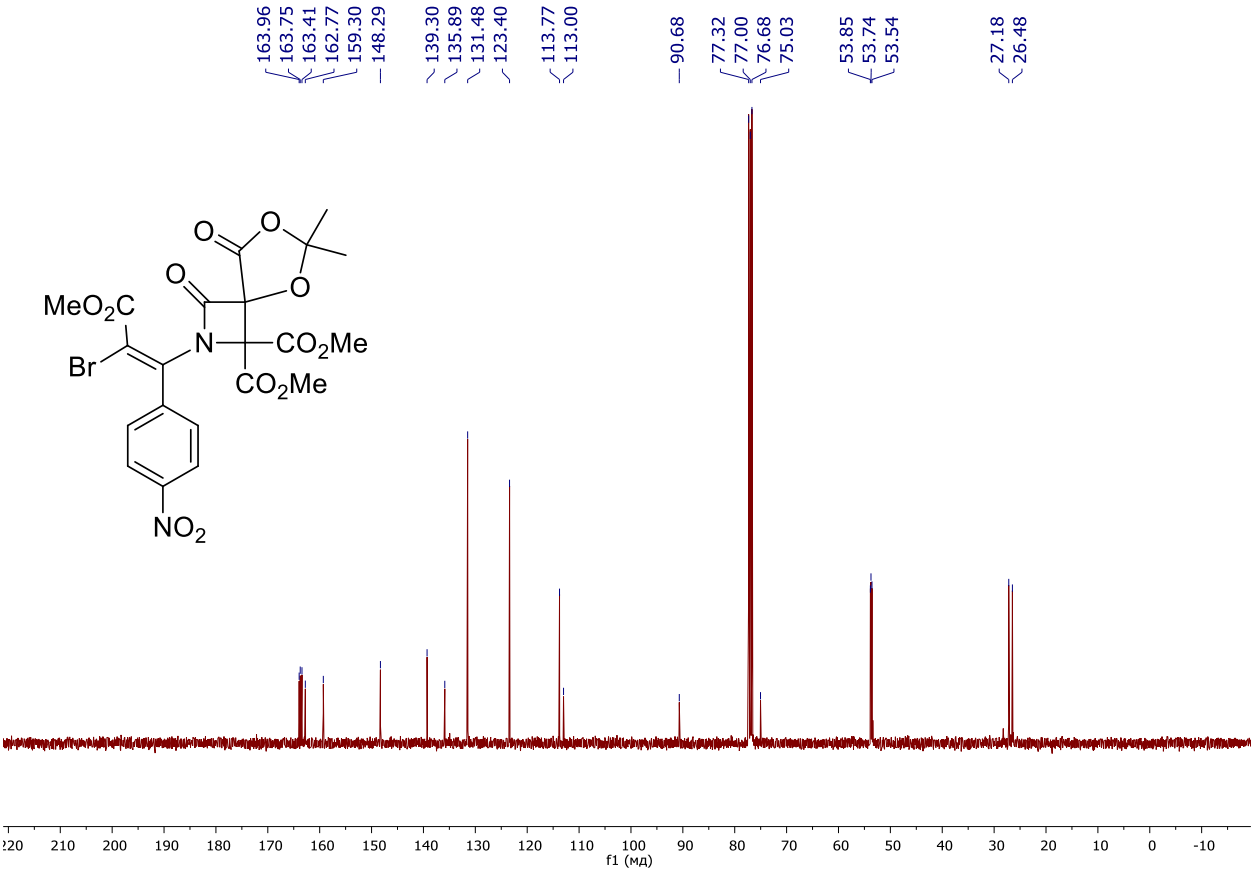


Dimethyl *(E)*-2-(2-bromo-1-(4-(tert-butyl)phenyl)-3-methoxy-3-oxoprop-1-en-1-yl)-6,6-dimethyl-3,8-dioxo-5,7-dioxa-2-azaspiro[3.4]octane-1,1-dicarboxylate (5l)

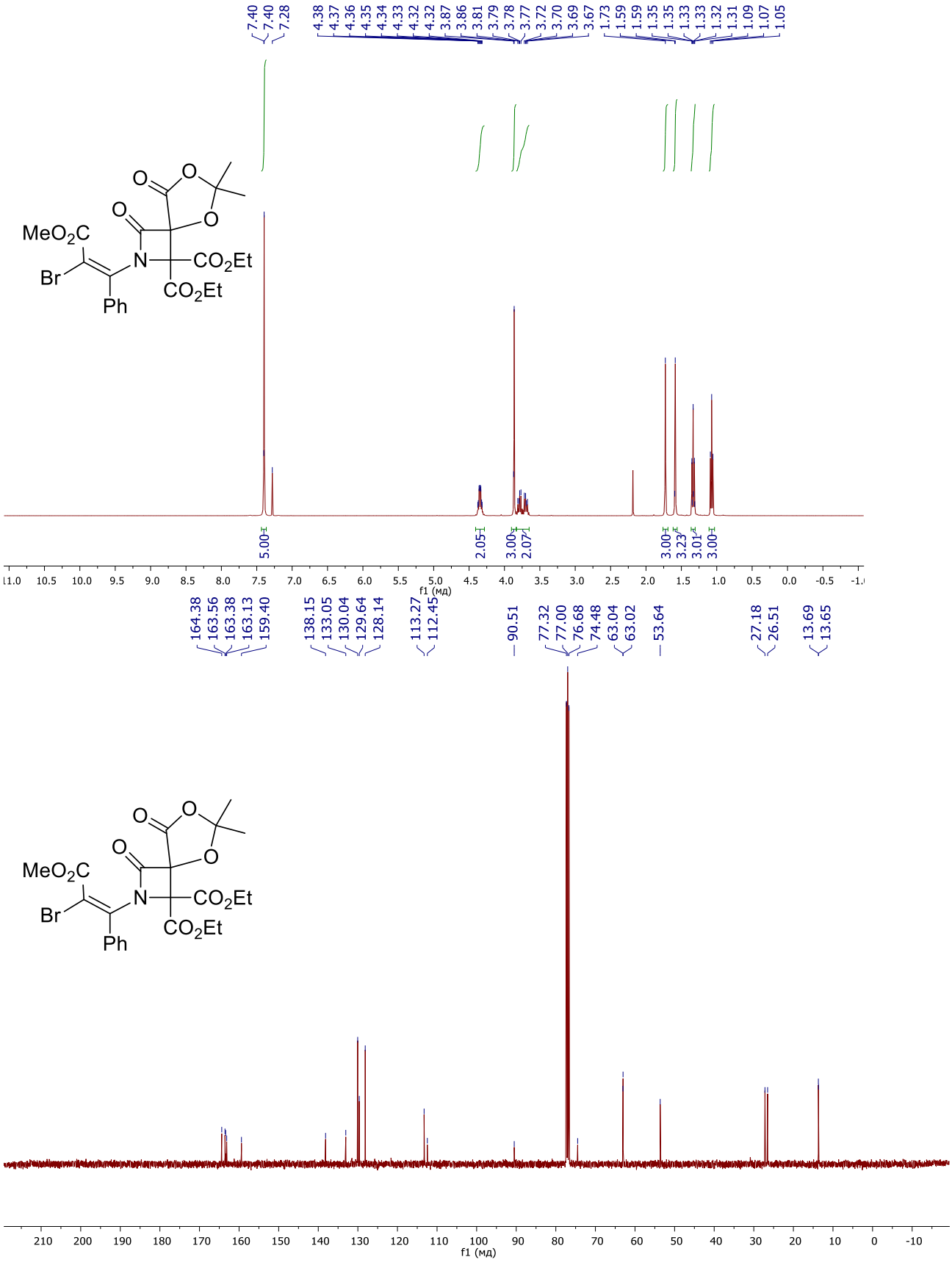


Dimethyl *(E)*-2-(2-bromo-3-methoxy-1-(4-nitrophenyl)-3-oxoprop-1-en-1-yl)-6,6-dimethyl-3,8-dioxo-5,7-dioxa-2-azaspiro[3.4]octane-1,1-dicarboxylate (5m)

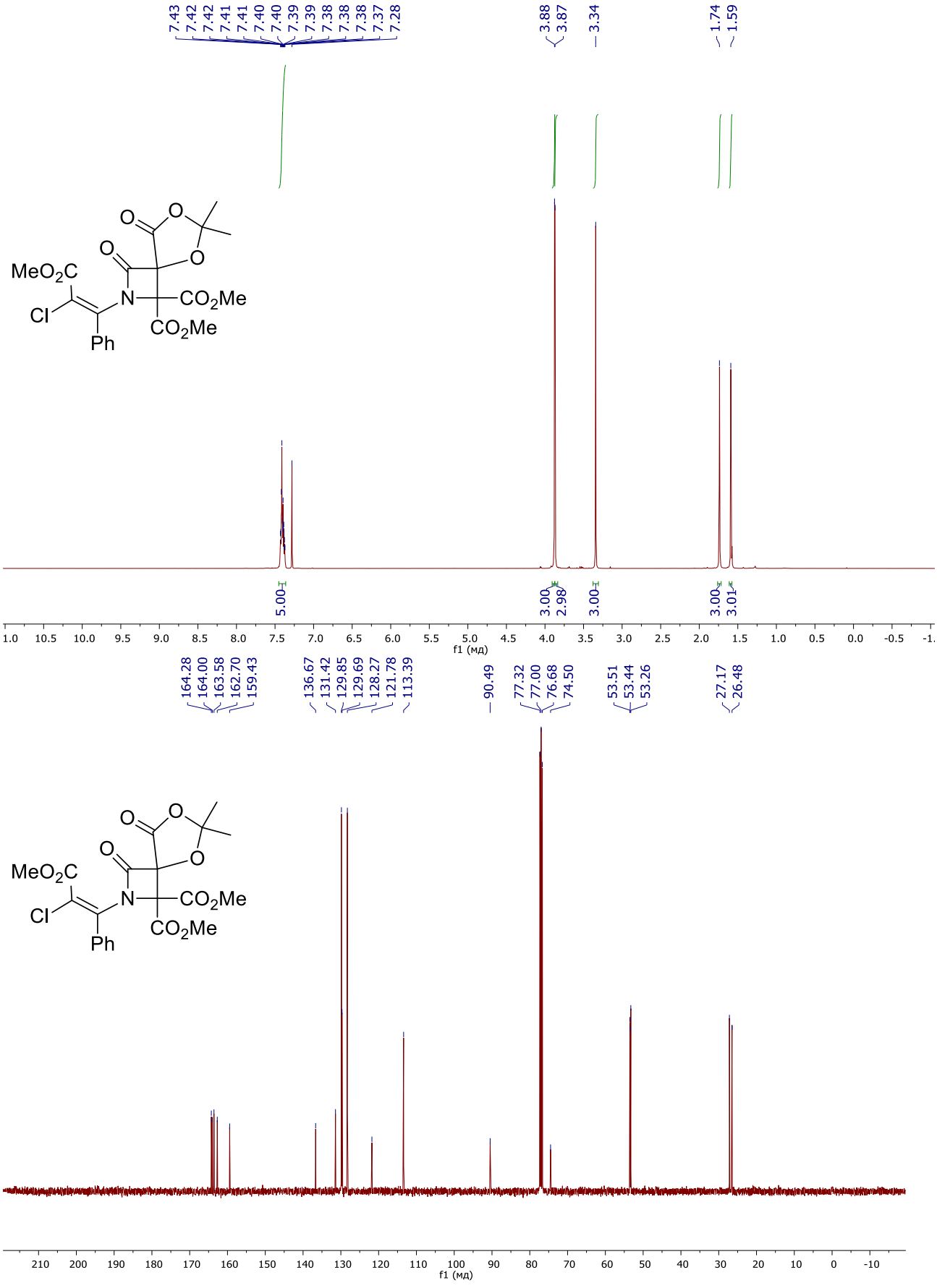




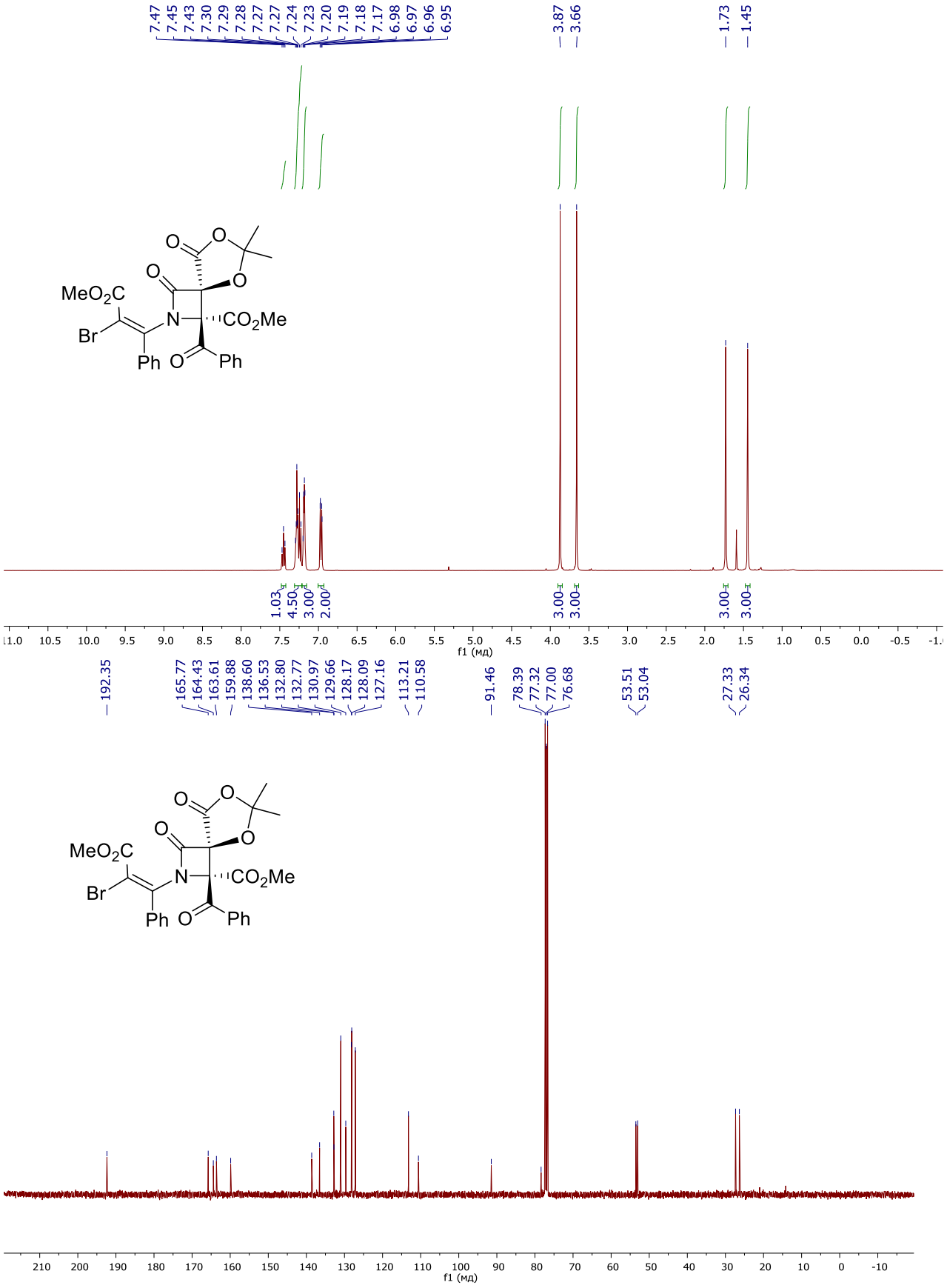
Diethyl *(E)*-2-(2-bromo-3-methoxy-3-oxo-1-phenylprop-1-en-1-yl)-6,6-dimethyl-3,8-dioxo-5,7-dioxa-2-azaspiro[3.4]octane-1,1-dicarboxylate (5n)



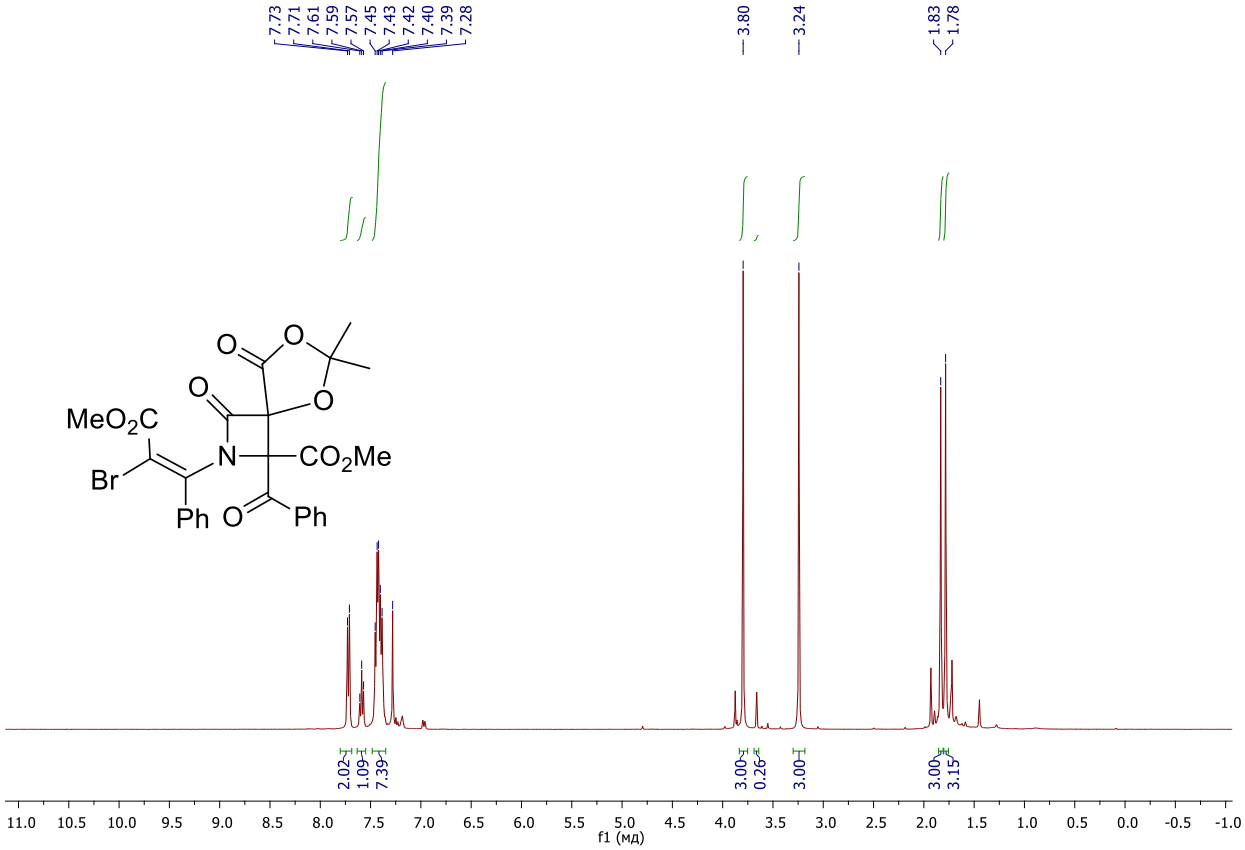
Dimethyl *(E)*-2-(2-chloro-3-methoxy-3-oxo-1-phenylprop-1-en-1-yl)-6,6-dimethyl-3,8-dioxo-5,7-dioxa-2-azaspiro[3.4]octane-1,1-dicarboxylate (5o)

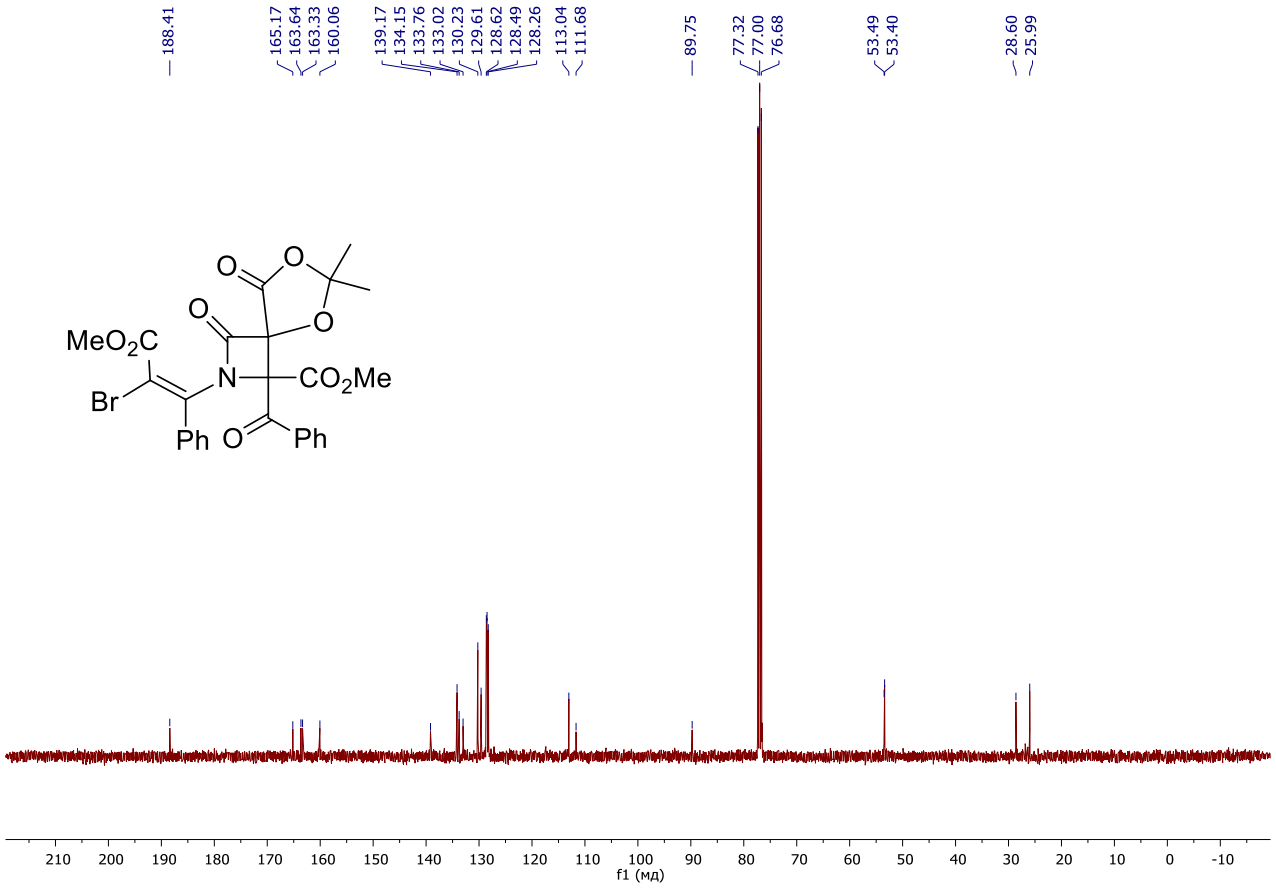


Methyl *(E)*-1-benzoyl-2-(2-bromo-3-methoxy-3-oxo-1-phenylprop-1-en-1-yl)-6,6-dimethyl-3,8-dioxo-5,7-dioxa-2-azaspiro[3.4]octane-1-carboxylate ((1*RS*,4*RS*)-5p)

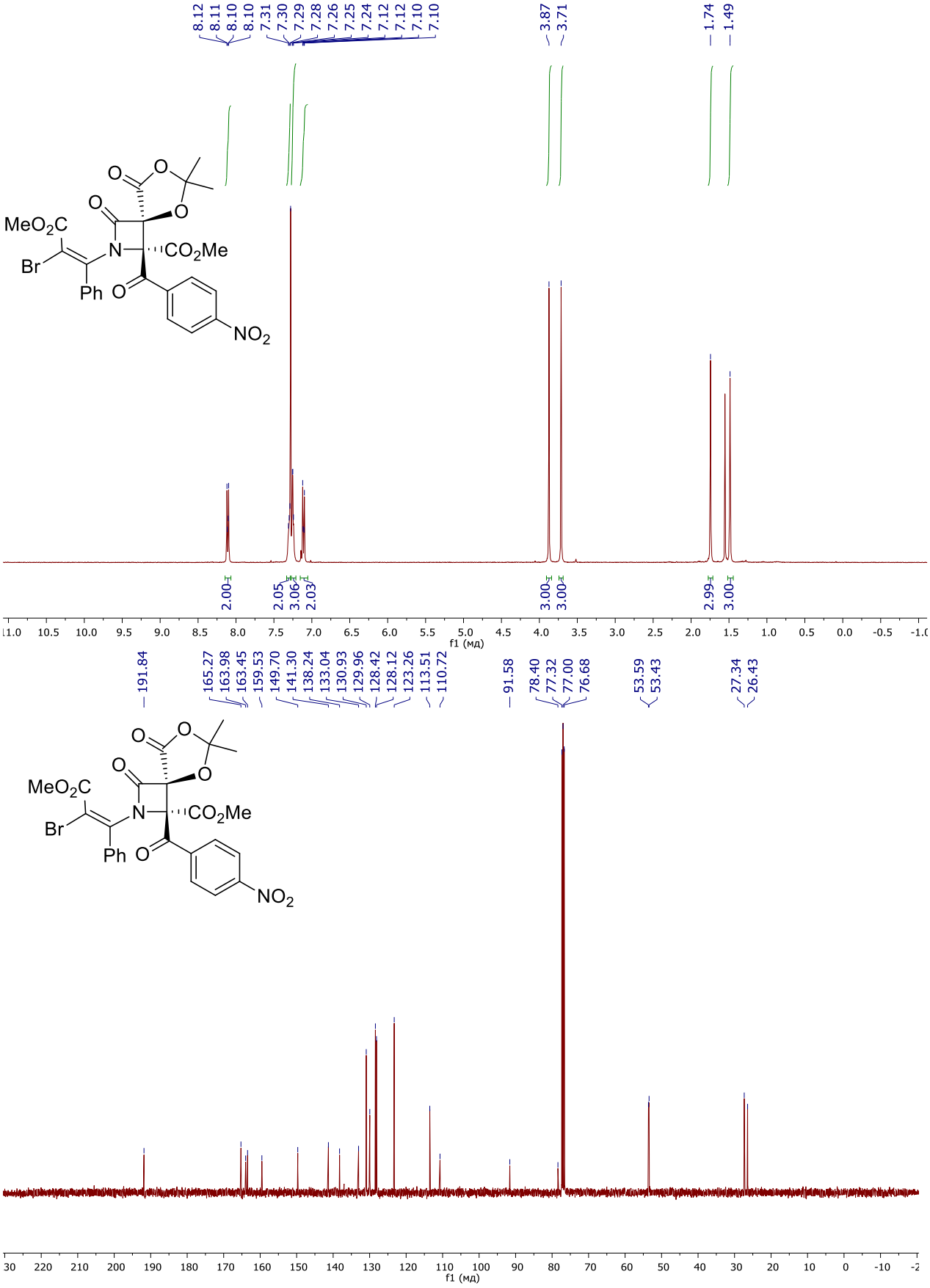


(1*RS*,4*SR*)-5p/(1*RS*,4*RS*)-5p mixture (10:1)

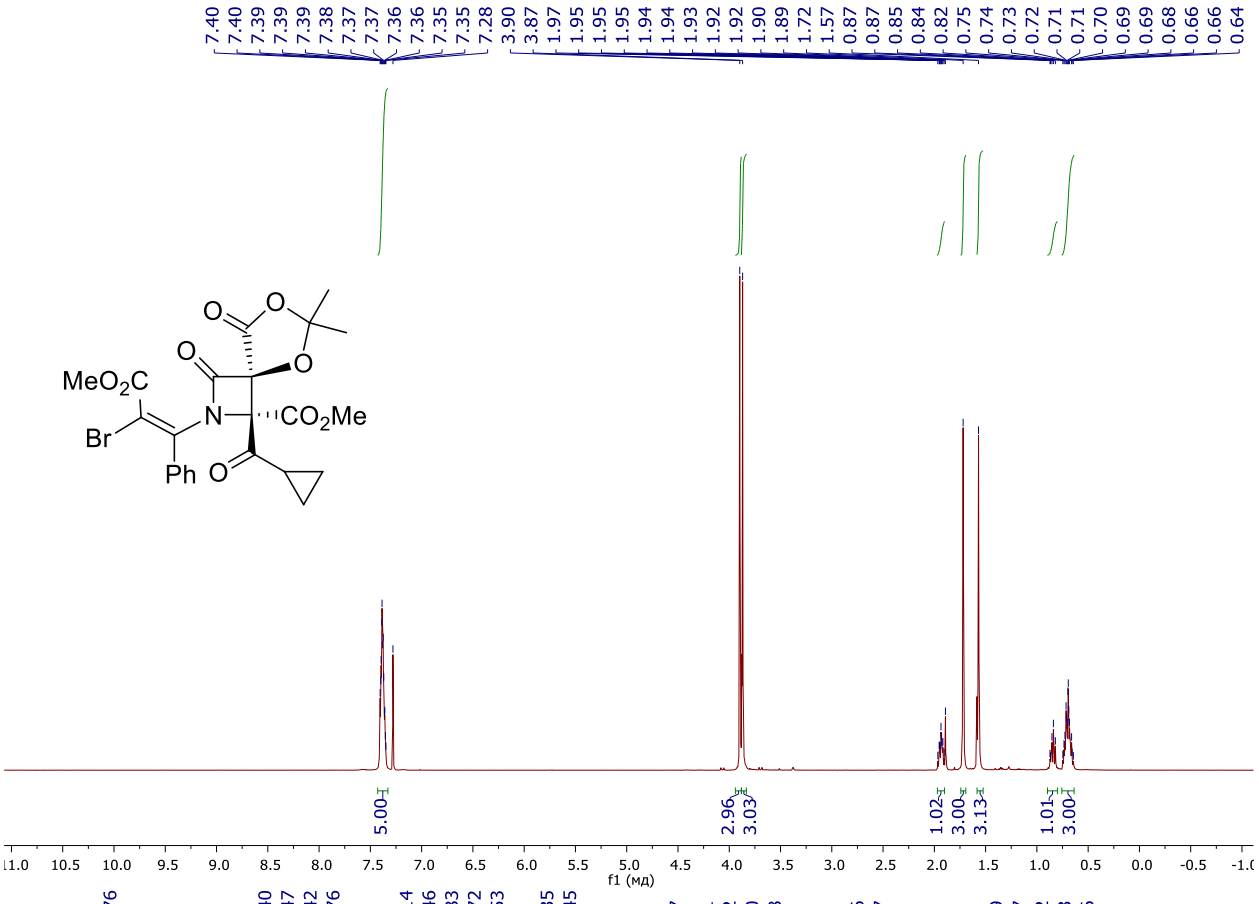


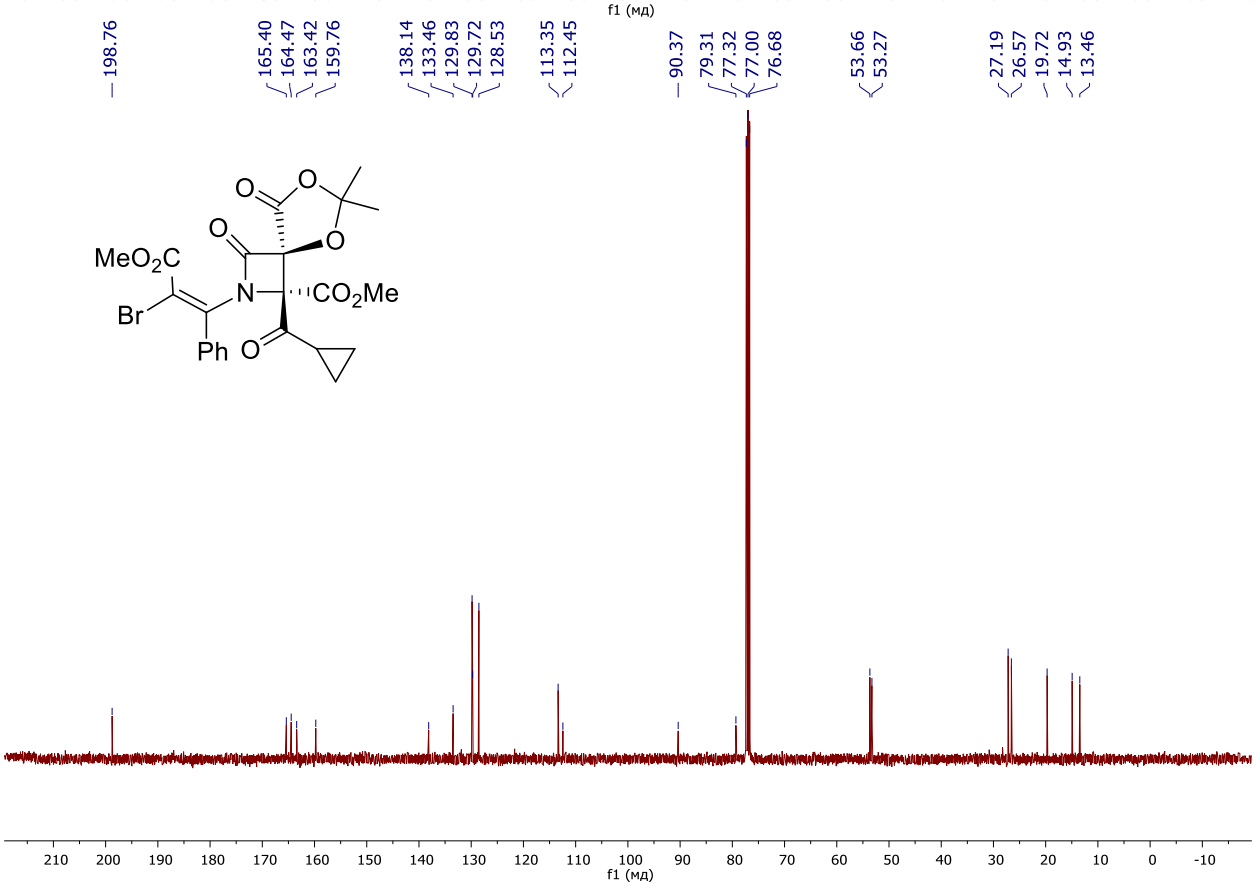


***(E)*-methyl 2-(2-bromo-3-methoxy-3-oxo-1-phenylprop-1-en-1-yl)-6,6-dimethyl-1-(4-nitrobenzoyl)-3,8-dioxo-5,7-dioxa-2-azaspiro[3.4]octane-1-carboxylate (5q)**

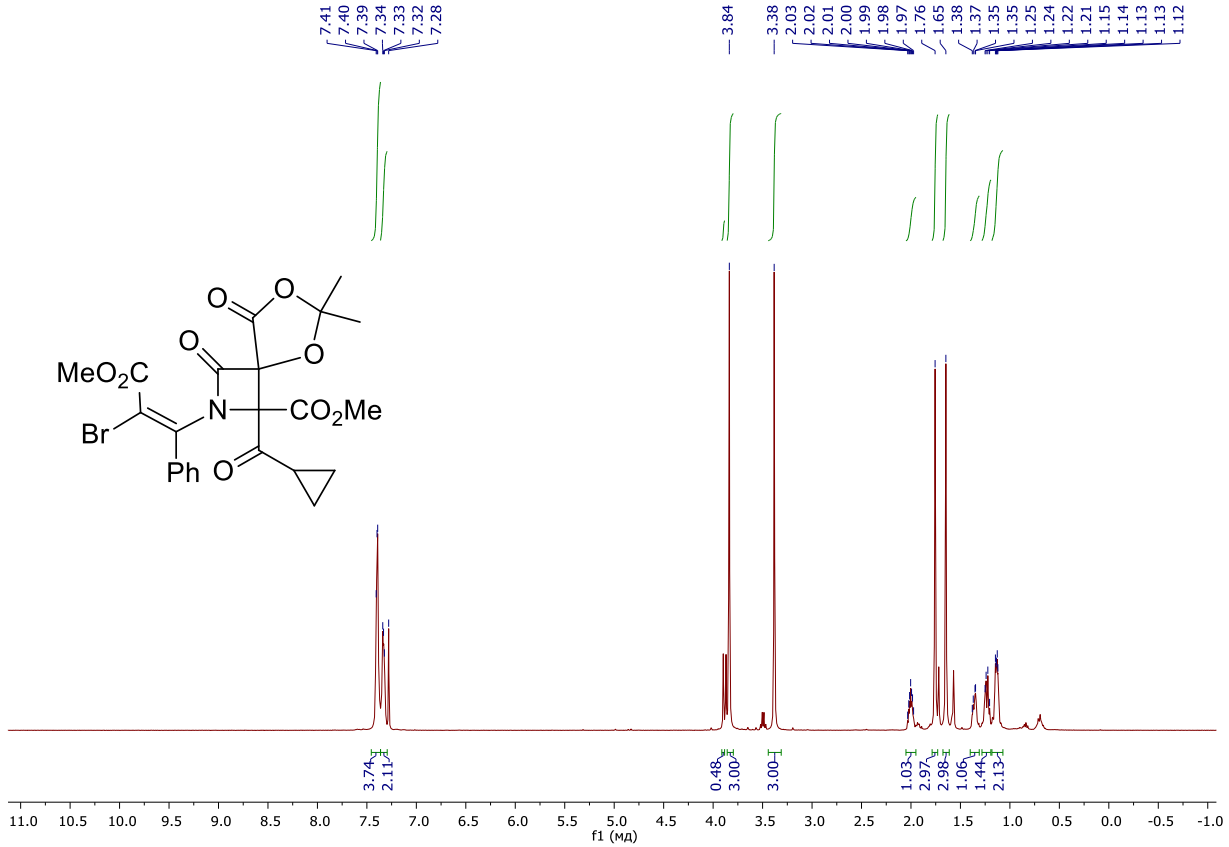


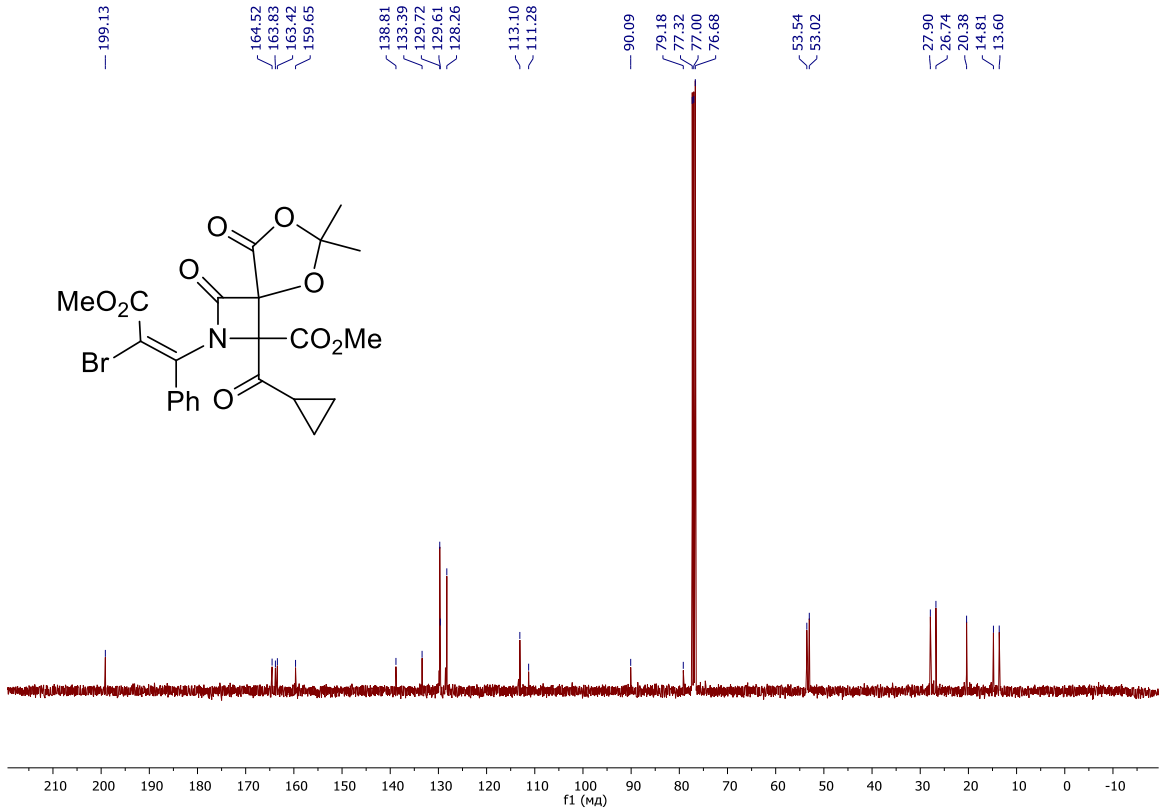
Methyl *(E)*-2-(2-bromo-3-methoxy-3-oxo-1-phenylprop-1-en-1-yl)-1-(cyclopropanecarbonyl)-6,6-dimethyl-3,8-dioxo-5,7-dioxa-2-azaspiro[3.4]octane-1-carboxylate ((1*RS*,4*RS*)-5r)



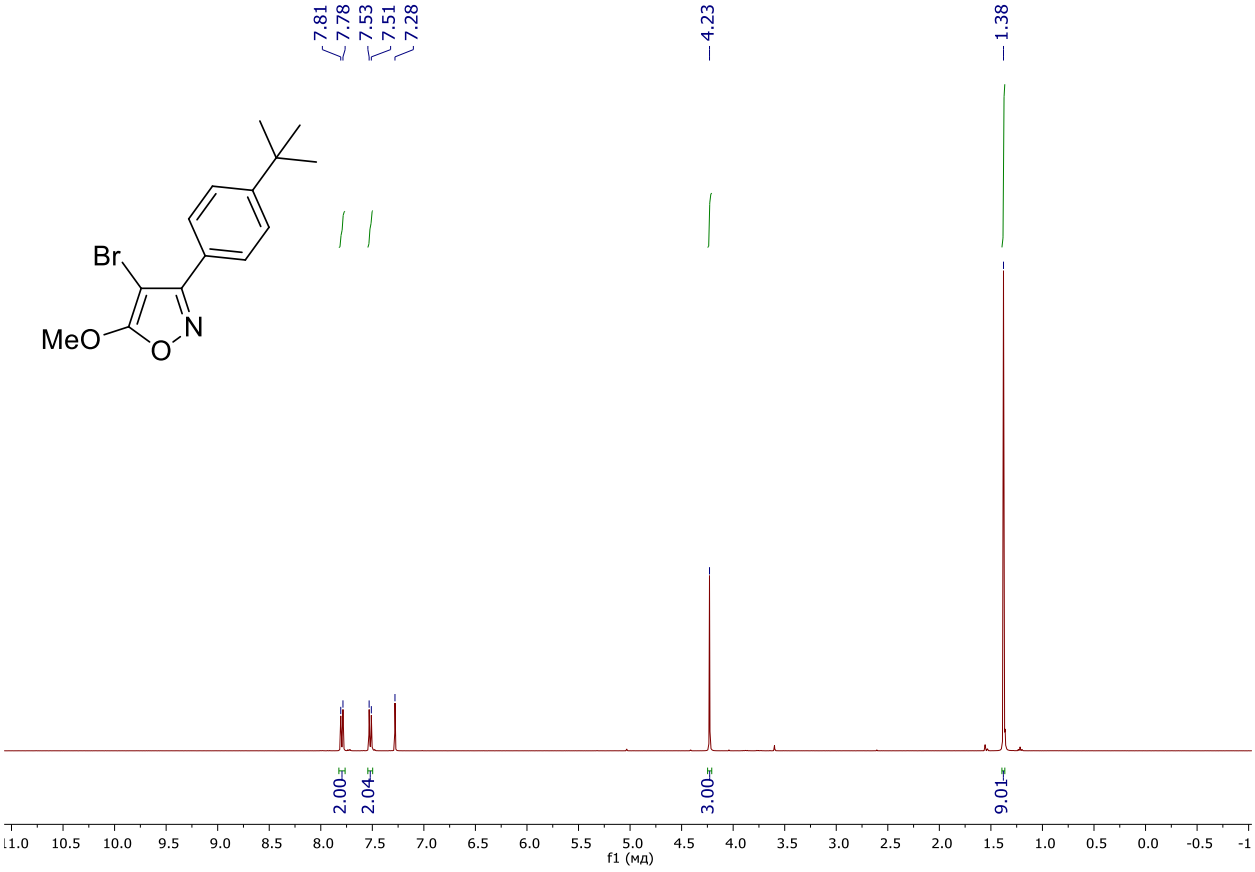


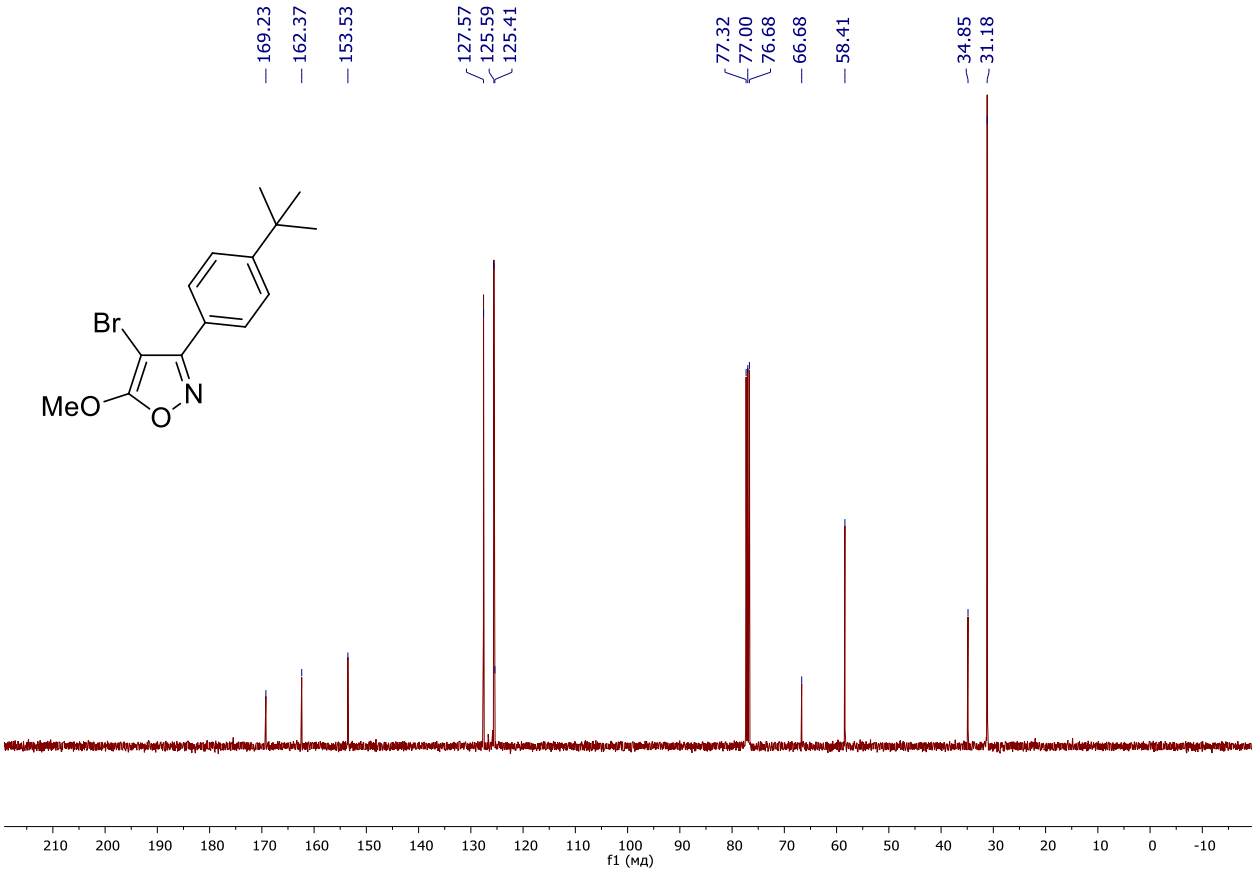
(1*RS*,4*SR*)-5r/(1*RS*,4*RS*)-5r mixture (6:1)



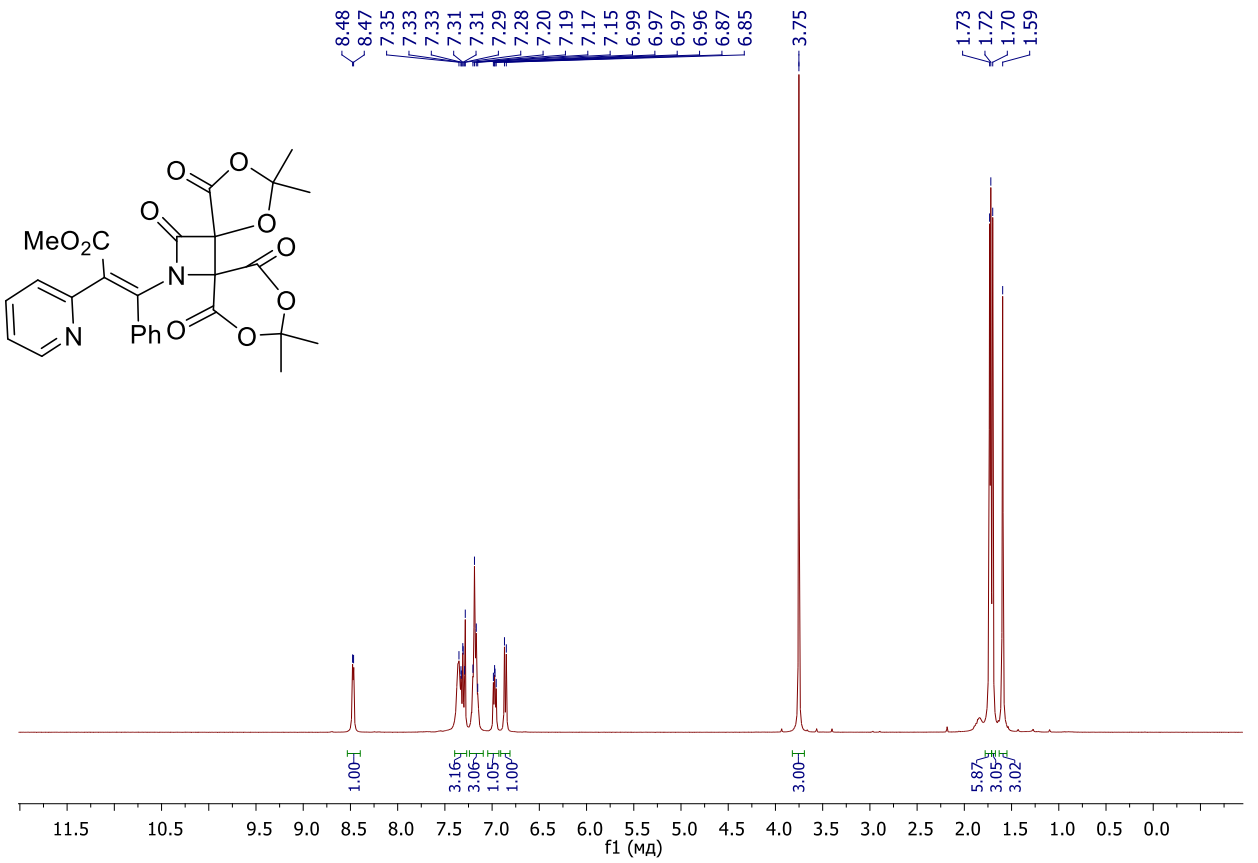


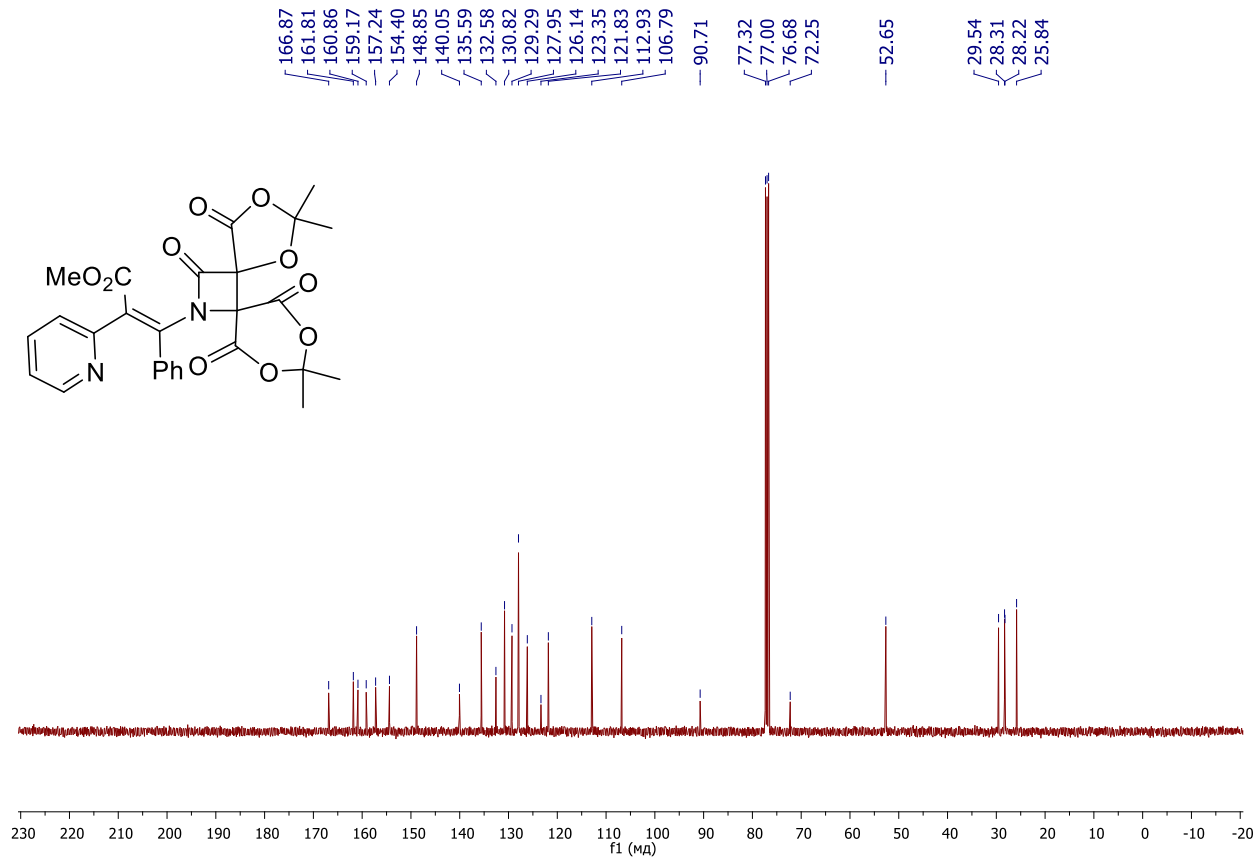
4-Bromo-3-(4-(*tert*-butyl)phenyl)-5-methoxyisoxazole (6f)





Methyl (*Z*)-2-(pyridin-2-yl)-3-phenyl-3-(2,2,9,9-tetramethyl-4,7,11,13-tetraoxo-1,3,8,10-tetraoxa-12-azadispiro[4.0.5^{6}.2^{5}]tridecan-12-yl)acrylate (12)





4. X-ray data of compounds 5a,p–r

Figure S1. X-Ray crystal structure of lactam **5a** with 50% ellipsoid probability (CCDC 1890947).

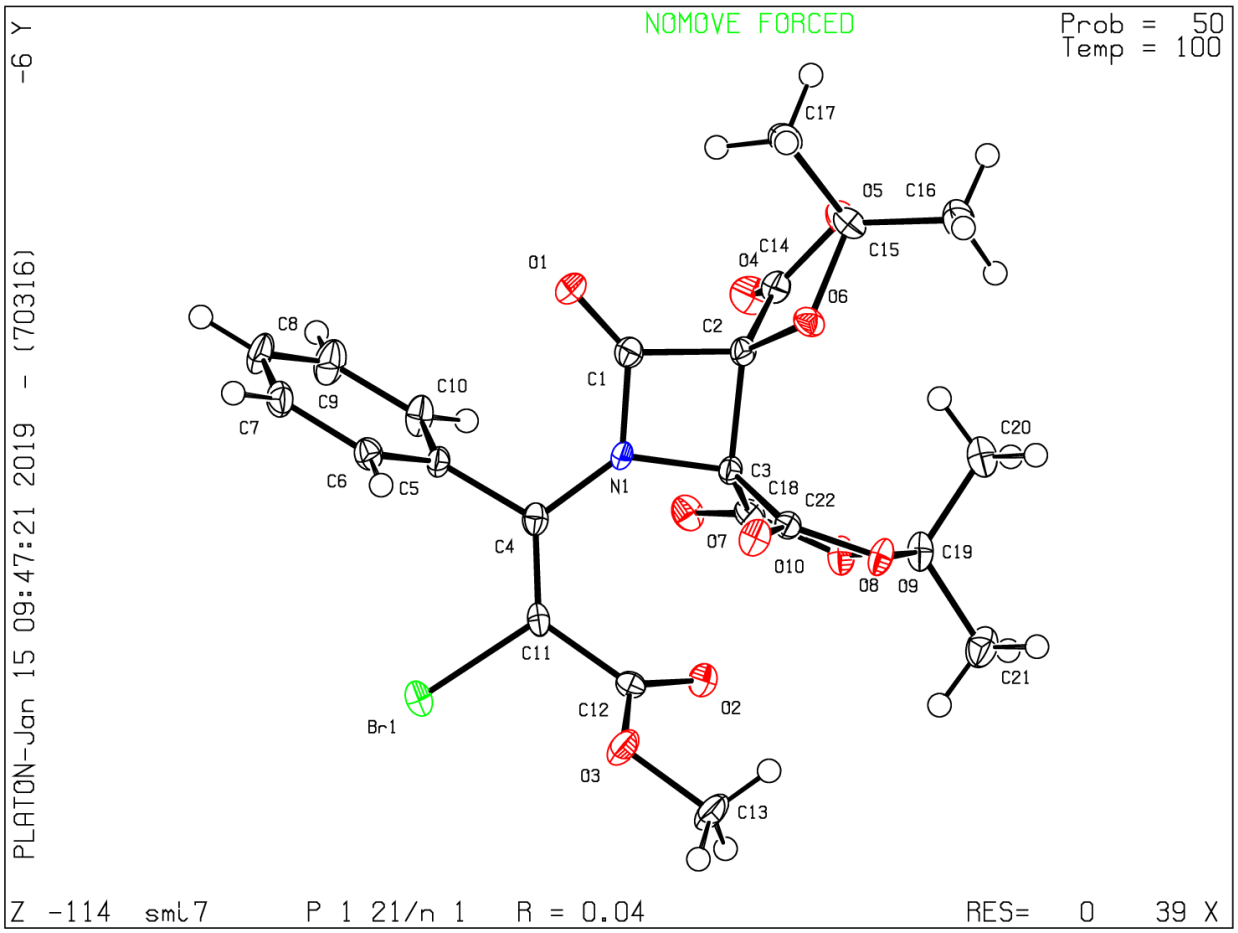


Table S1. Crystal data and structure refinement for compound **5a**.

Identification code	smi7
Empirical formula	$C_{22}H_{20}NO_{10}Br$
Formula weight	538.30
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	9.6963(3)
b/Å	12.8666(3)
c/Å	18.3433(6)
α/°	90
β/°	100.842(3)
γ/°	90
Volume/Å^3	2247.61(12)
Z	4
ρ_{calc}g/cm^3	1.591
μ/mm^{-1}	1.888
F(000)	1096.0
Crystal size/mm^3	0.26 × 0.20 × 0.16
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.2 to 54.988
Index ranges	$-11 \leq h \leq 12$, $-16 \leq k \leq 16$, $-23 \leq l \leq 23$
Reflections collected	22363
Independent reflections	5104 [R_{int} = 0.0392, R_{sigma} = 0.0386]
Data/restraints/parameters	5104/0/312
Goodness-of-fit on F^2	1.047
Final R indexes [I>=2σ (I)]	R_1 = 0.0380, wR_2 = 0.0743
Final R indexes [all data]	R_1 = 0.0509, wR_2 = 0.0790
Largest diff. peak/hole / e Å^{-3}	1.19/-0.55

Figure S2. X-Ray crystal structure of lactam **5p** with 50% ellipsoid probability (CCDC 1811691).

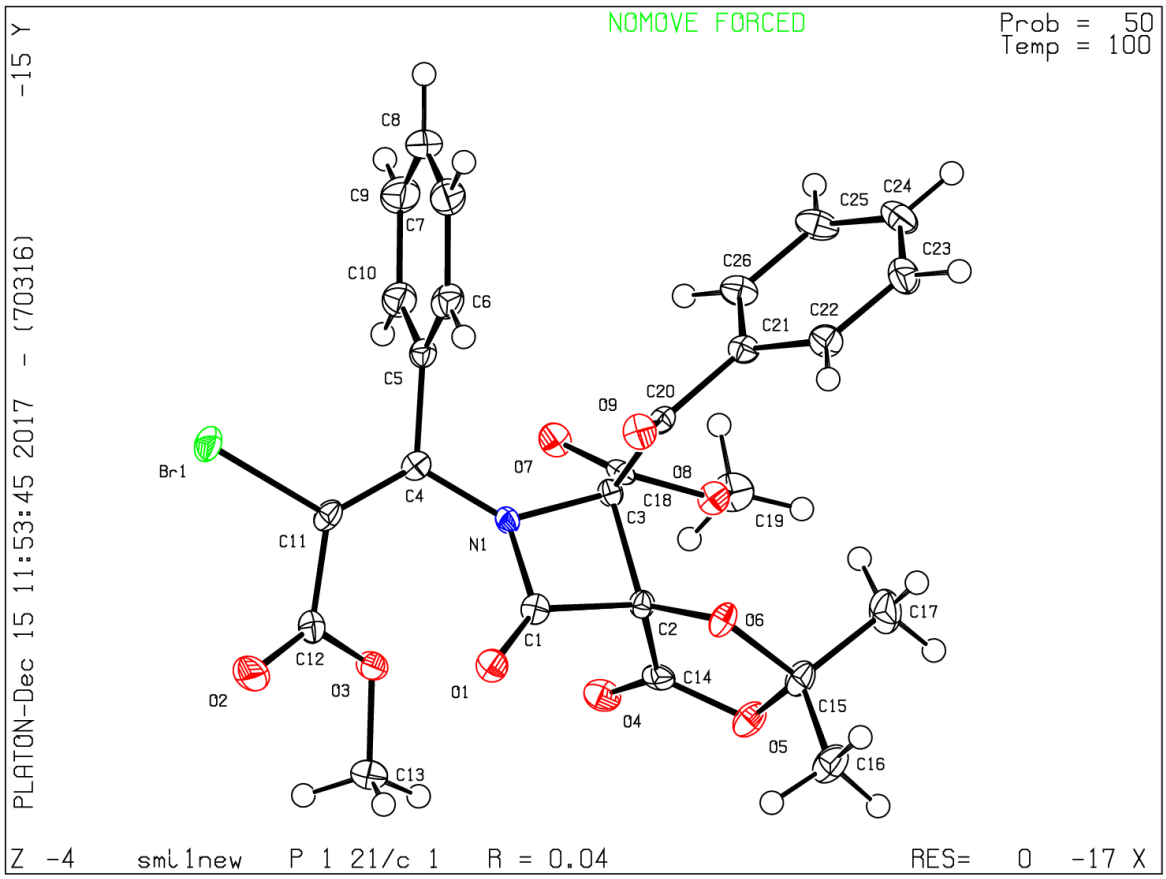


Table S2. Crystal data and structure refinement for compound **5p**.

Identification code	smi1new
Empirical formula	$C_{26}H_{22}NO_9Br$
Formula weight	572.35
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.2685(6)
b/Å	18.6581(7)
c/Å	12.8795(8)
α/°	90
β/°	111.426(7)
γ/°	90
Volume/Å^3	2520.8(2)
Z	4
ρ_{calc}g/cm^3	1.508
μ/mm^{-1}	1.686
F(000)	1168.0
Crystal size/mm^3	0.28 × 0.16 × 0.12
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.532 to 54.996
Index ranges	$-13 \leq h \leq 14$, $-22 \leq k \leq 24$, $-12 \leq l \leq 16$
Reflections collected	10736
Independent reflections	5709 [R_{int} = 0.0324, R_{sigma} = 0.0557]
Data/restraints/parameters	5709/0/338
Goodness-of-fit on F^2	1.030
Final R indexes [I>=2σ (I)]	R_1 = 0.0388, wR_2 = 0.0764
Final R indexes [all data]	R_1 = 0.0592, wR_2 = 0.0845
Largest diff. peak/hole / e Å^{-3}	0.66/-0.47

Figure S3. X-Ray crystal structure of lactam **5q** with 50% ellipsoid probability (CCDC 1893280).

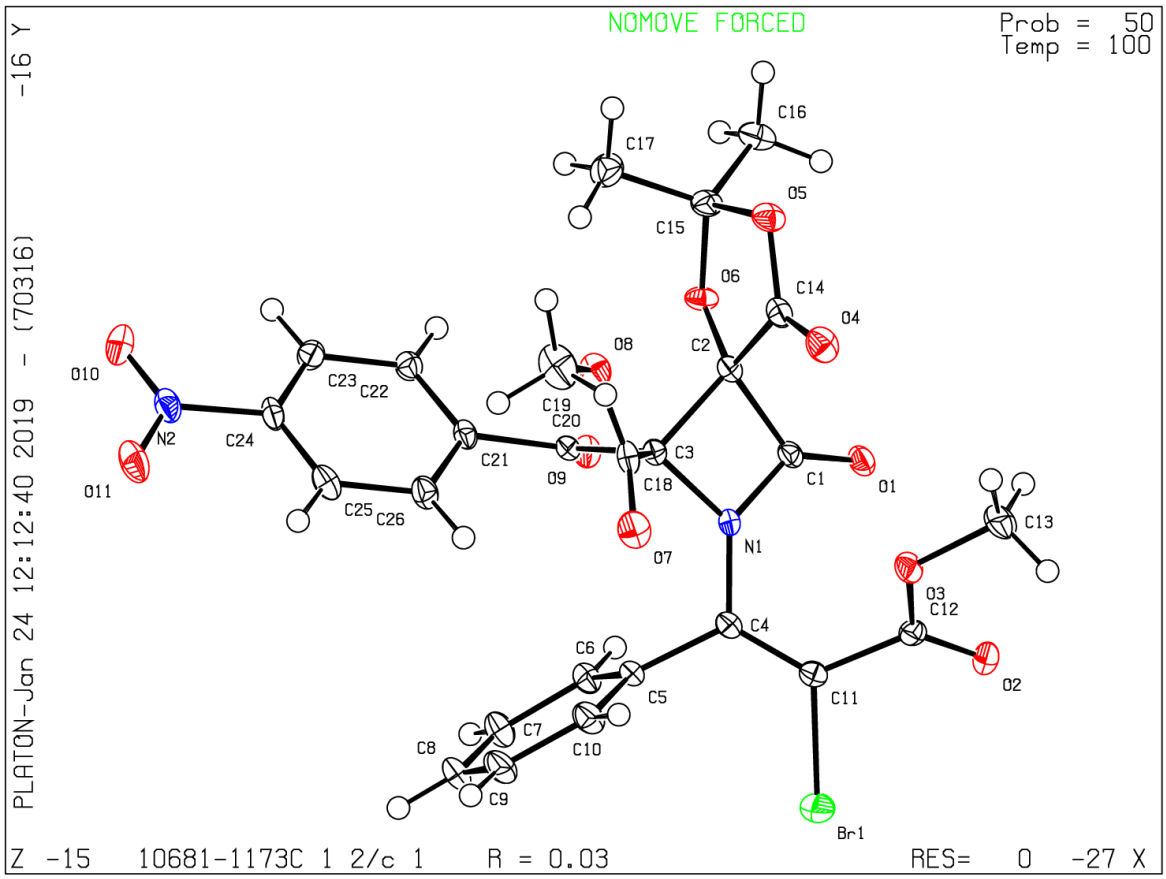


Table S3. Crystal data and structure refinement for compound **5q**.

Identification code	10681-11733_agf2
Empirical formula	$C_{26}H_{21}BrN_2O_{11}$
Formula weight	617.36
Temperature/K	100(2)
Crystal system	monoclinic
Space group	C2/c
a/Å	17.9781(2)
b/Å	10.33117(14)
c/Å	27.7978(4)
α/°	90
β/°	93.5433(12)
γ/°	90
Volume/Å^3	5153.15(12)
Z	8
ρ_{calc}g/cm^3	1.591
μ/mm^{-1}	2.770
F(000)	2512.0
Crystal size/mm^3	0.26 × 0.16 × 0.12
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.372 to 152.302
Index ranges	$-22 \leq h \leq 22$, $-12 \leq k \leq 12$, $-34 \leq l \leq 34$
Reflections collected	34103
Independent reflections	5332 [R_{int} = 0.0301, R_{sigma} = 0.0181]
Data/restraints/parameters	5332/0/365
Goodness-of-fit on F^2	1.064
Final R indexes [I>=2σ (I)]	R_1 = 0.0346, wR_2 = 0.0979
Final R indexes [all data]	R_1 = 0.0356, wR_2 = 0.0988
Largest diff. peak/hole / e Å^{-3}	0.50/-0.93

Figure S4. X-Ray crystal structure of lactam **5r** with 50% ellipsoid probability (CCDC 1893285).

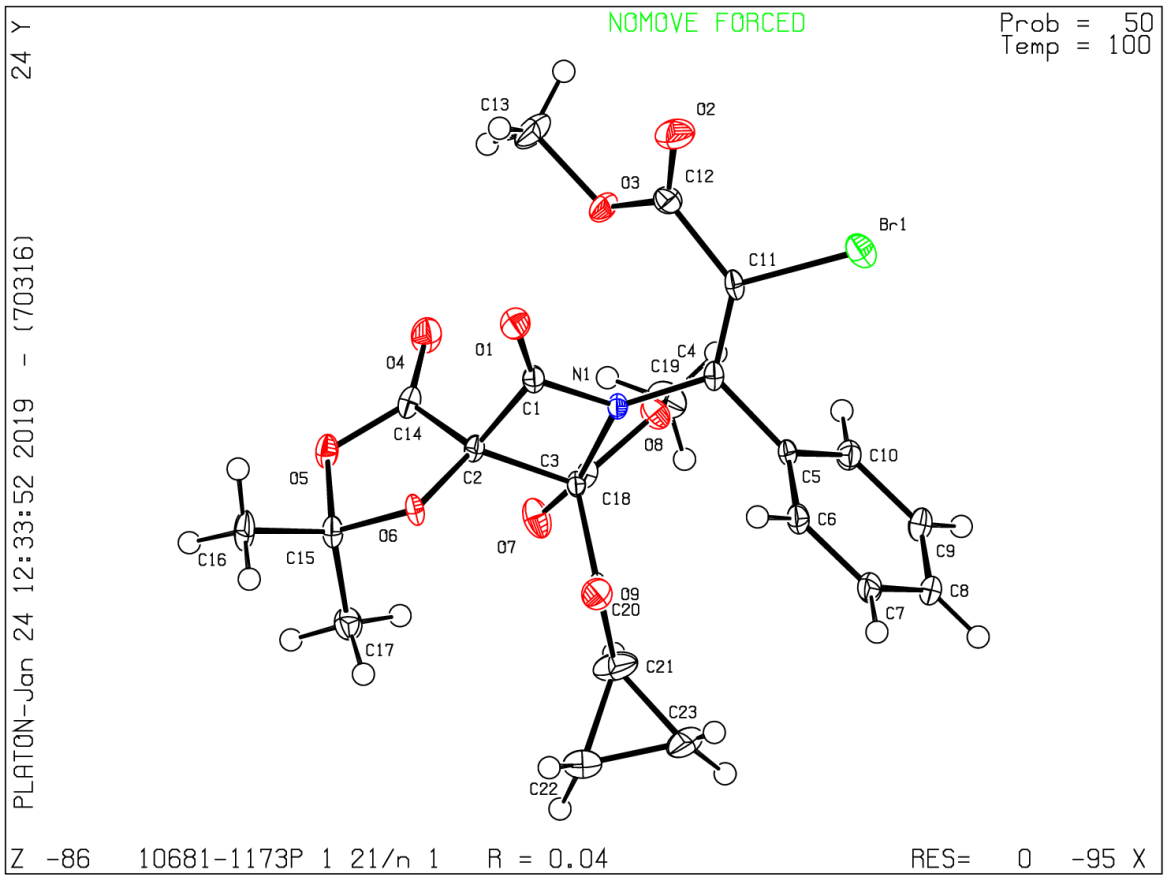


Table S4. Crystal data and structure refinement for compound **5r**.

Identification code	10681-11733_agf1
Empirical formula	$C_{23}H_{22}BrNO_9$
Formula weight	536.32
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	11.66080(10)
b/Å	15.21840(10)
c/Å	13.20380(10)
α/°	90
β/°	91.1330(10)
γ/°	90
Volume/Å^3	2342.67(3)
Z	4
ρ_{calc}g/cm^3	1.521
μ/mm^{-1}	2.867
F(000)	1096.0
Crystal size/mm^3	0.24 × 0.16 × 0.14
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.868 to 145.802
Index ranges	-14 ≤ h ≤ 13, -18 ≤ k ≤ 18, -15 ≤ l ≤ 16
Reflections collected	23811
Independent reflections	4641 [R_{int} = 0.0294, R_{sigma} = 0.0163]
Data/restraints/parameters	4641/0/312
Goodness-of-fit on F^2	1.087
Final R indexes [I>=2σ (I)]	R_1 = 0.0398, wR_2 = 0.1143
Final R indexes [all data]	R_1 = 0.0402, wR_2 = 0.1147
Largest diff. peak/hole / e Å^{-3}	0.55/-1.19

5. References

1. N. V. Rostovskii, A. V. Agafonova, I. A. Smetanin, M. S. Novikov, A. F. Khlebnikov, J. O. Ruvinskaya, G. L. Starova, *Synthesis*, 2017, **28**, 4478–4488.